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To add life to years, not just years to life

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JOURNAL OF GERONTOLOGY

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The Relationship of Medical Practice to Gerontology*

JAMES E. PAULLIN

GERIATRICS, ALTHOUGH A COMPARATIVELY OLD BRANCH OF MEDICAL SCIENCE, HAS ONLY WITHIN THE PAST FIFTEEN TO TWENTY YEARS OCCASIONED MUCH COMMENT OR STUDY. AGING HAS BEEN KNOWN TO BEGIN AT THE TIME OF CONCEPTION, BUT THE AGING PROCESS HAS GENERALLY BEEN ACCEPTED AS ROUTINE AND LITTLE HAS BEEN DONE TO MEET THE PROBLEMS PRESENTED BY ALTERATIONS IN THE PHYSIOLOGIC, BIOLOGIC, AND CHEMICAL PROCESSES INVOLVED. THE EXTENSION OF LENGTH OF LIFE TODAY HAS BEEN BROUGHT ABOUT CHIEFLY BY PEDIATRICIANS IN ESTABLISHING BETTER CONTROL OF INFECTIOUS DISEASE. THE PURPOSE OF GERIATRICS IS NOT TO SEEK THE PROLONGATION OF LIFE AS MUCH AS IT IS TO SEE THAT THE LIVES OF THOSE WHO ARE AGING ARE MADE MORE EFFECTIVE BY PREVENTING, DELAYING, OR DIMINISHING THE PROGRESS OF THE DEGENERATIVE STATE.

THE science of aging as it affects all animate and inanimate objects is gerontology. In journeying here and there, many people are conscious of the effects of the passage of time on various objects. The strong, sturdy mountain is seen gradually yielding to the effects of heat, cold, rain, snow and sunshine; the house in which one lives gradually disintegrates from forces operating from without similar to the forces affecting the mountains, and in addition there are other destructive agents such as use and abuse, as well as those acquired, such as termites. The same forces, with others added, are effective against the life and usefulness of man.

During the past several years attention has been more sharply focused on the process of growing old because it was necessary to conserve all material resources to supply the immediate demands of prosecuting successful warfare. For this reason people were made conscious of the destructive effect of abuse and lack of care on the various mechanical contrivances considered desirable and necessary for their standard of living. For example, in the use of automobiles people were told that in order to conserve the supply of gasoline, oil, tires, and the replaceable parts of a car it was necessary that speed be lowered to a determined mileage per hour in order to prolong the period of usefulness of automobiles as well as to decrease accidents. Necessity forced this upon us, because most of the essentials, such as tires and parts, could not be replaced; however, to further enforce this conservation periodic inspection of tires by an official agency of the government was made mandatory, and certificates of such inspection had to be presented before coupons for the purchase of gas would be issued. This is a timely illustration of what can be accomplished in prolonging the usefulness of an automobile. Could man not profit by similar regulations?

Having been engaged in the active prac-

* Delivered February 14, 1946, as a part of the Third Annual Medical and Surgical Symposium sponsored by the Watts Hospital Staff of Watts Hospital, Durham, North Carolina.

Dr. James E. Paullin is professor of clinical medicine at Emory University Medical School and has worked almost exclusively in the field of internal medicine. He graduated from Mercer University in Macon, Georgia, in 1900 and received his M.D. degree from Johns Hopkins University in 1905. He holds an honorary LL.D. from Mercer and from Emory University. He is a former president of the American Medical Association and the American College of Physicians, is honorary consultant to the Surgeon General of the United States Navy, and has been decorated with the Order of Carlos Finlay by President Batista of Cuba.

tice of medicine for quite a few years, as well as having occupied a teaching position in the department of medicine of Emory University, I have accumulated records of a large number of patients representing all ages and dealing with many problems of health as well as disease. I have been fortunate in being able to follow quite a few of these patients more or less continuously for decades. Some have been observed from the period of adolescence, through middle age, to the older age group. The effect upon the body of the wear and tear of living, as well as that of disease, has been observed and recorded. Advantage is taken of this occasion to express some of the thoughts which have come to me from a more or less casual perusal of these records. Unfortunately I haven't had the time, nor the opportunity, of giving careful study to many observations that such an occasion as this demands, but perhaps these remarks may stimulate a sufficient amount of interest among this audience that you too will participate in a similar study. It is my hope in the near future to begin, from the clinical point of view, a study of the problem of aging.

The responsibility for initiating a study of the problems of aging and stimulating research concerning many of the questions they suggest is an ever increasing one. Geriatrics is that division of the medical sciences which concerns itself with the diseases encountered in, and responsible for, the acceleration of disability and death in those who are aging. This division of medicine, although comparatively old, has only within the past fifteen or twenty years occasioned much comment or study.

The process of aging begins immediately after conception, but only after birth can disuse and atrophy be observed. Disuse is represented by the disappearance of the ductus arteriosus, which occurs at birth, and atrophy of the thymus gland begins shortly after birth. Then come growth and evolutionary changes which eventually lead to the maturation of the individual as a person. Following or concomitant with maturation and again with the passage of time, involutional changes occur which cause a decline of bodily functions and the diminution or cessation of other activities which eventually lead to senility. Most people have accepted this aging process as routine, or the usual course of events, and have done very little to meet the problems presented by alterations in the physiologic, biologic, chemical and physical processes involved.

In 1900, life expectancy in the United States was 47 years. In 1940 it was 63 years. This extension of sixteen years has been due chiefly to the accomplishments of the pediatricians in establishing better control of infectious diseases, in the lowering of infant mortality, and in the adoption of better methods for the treatment and cure of disease. No longer can it be said that the prolongation of the life span is due to the survival of the fittest. Present day methods have made possible the survival of a great many children who are now, or soon will be, unfit to meet the problems of living. No better proof of this could be offered than the data submitted by Selective Service Boards, pointing out the many physical and mental defects found among the draftees in World War II. Some of these defects were preventable, some remediable, others represent constitutional

inadequacy and inherent weaknesses which sooner or later will make those so afflicted totally unfit for service and a financial burden on the family or government. Already there is a large group in this category showing premature evidence of pathologic aging and requiring an increasing amount of medical care.

Not only has there been an increase in the years of life expectancy, but there has has been a marked increase in the number of persons in the decades beyond 50. Since World War II this increase in older people will be accentuated, which means an increase in those who will develop arteriosclerosis, hypertension, arteriosclerotic heart disease, chronic nephritis, diabetes, cancer, the arthritides, degenerative diseases of the nervous system, and many other diseases of age. There will also remain a very large group who show only the normal amount of wear and tear from ordinary living. Why should there be such a difference numerically between these groups? I will come back to this later.

At this point it might be well to give expression to what might be considered a reasonable chronologic approach to the groups undergoing aging.

Group 1. The period of development from birth to age 20.

Group 2. The period of maturity from ages 20 to 40.

Group 3. The period of decline from ages 40 to 60.

Group 4. The period of senility from 60 years onward.

It is true that no hard and fast rule can be made in classifying every individual into one of the above categories, for it is well known that some people at 40 show changes characteristic of those at 60, while many people of 60 years and over maintain all of the vim, vigor, and mental alertness of the younger group.

Aging is a process which follows fairly well defined paths. At the same time it has been observed that its effect on people is influenced by many factors, such as infections, intoxications, methods and manner of living, and other life experiences. One cannot but be impressed by the increasing evidences of aging which have been shown by many elderly people who have gone through the anxieties, sorrows, and burdens of World War II; with relief from the anxiety since V-J Day, the already initiated aging has not diminished its tempo. Again using as an illustration the automobile tire, it cannot be said that all tires made by the same manufacturer are capable of giving the same amount of service; they may look alike and are all good up to a certain point, but then they begin to manifest defects; their usefulness depends on the quality of the fabric and the materials of which they are made, together with the care used in their construction. These are the factors which determine the amount of punishment the tire can withstand without blowing out. With human beings, those who start life with good material handed down by ancestors are able to weather many storms without great damage, but the number of storms that can be withstood depends also on the care used in going through them. Heredity determines to a greater extent than any other factor how well a person stands aging.

Certain evidences of aging are observed rather easily. A person is called old if he has gray hair, stooped shoulders, loss of weight, slight impairment of hearing, presbyopia, loss of subcutaneous fat, wrinkling, loss of elasticity, increase of pigmentation, or the development of keratoses of the skin, decalcification of the bone, emphysema, impairment of memory, and inability to respond rapidly to sudden changes of stress and strain. Is there an answer to what accelerates or retards these changes? While there is no known answer there are many speculative possibilities, most of which must be related to chemical processes occurring within the tissues and organs of the body which influence the nutrition of the individual cell or collection of cells, as well as the resistance which the cell or the

cellular system is capable of offering against chemical changes. Physicians do not know, or at least I am not familiar with any definite pronouncement which has been made concerning, the *modus operandi* of such processes, yet it is justifiable to assume that the question of nutrition is vitally concerned in any disturbance of physiologic workings during the aging period. What is the disturbance of nutrition at fault? Do people fail to consume an adequate diet, well distributed as to its content of carbohydrate, protein, fat, vitamins and minerals, or does the fault lie with poor digestion, absorption, or utilization of these foods? Certainly in this day and time one could hardly suppose that anyone living within the sound of a radio would dare go without his quota of vitamins, whether needed or not. Vitamins happen to be at the present time the universal fad, and there is scarcely a day that passes that patients do not first inform their physicians that they have been taking their vitamins regularly as advised by the radio announcer, but that they are no better and would like further advice. Yet aging goes merrily on.

What part is played by the endocrine glands in the acceleration or retardation of the aging processes? If the report of one case by Paul de Kruif, a personal experience with testosterone proprionate, as rereported in the *Reader's Digest*, could be accepted as universal, the search might not have to be pursued further, but perhaps Mr. de Kruif has not completely evaluated his aging and he might have misinterpreted some of his objective experiences. Unquestionably the diminution or the cessation of certain secretory products of the endocrine glands plays a part in aging, but maybe a very small part. Many other suggestions might be made of factors which influence the behavior of the body from day to day. The question naturally arises: Can a standard be established based on present knowledge, by which the physiologic needs of a given individual can be judged so that aging will proceed in an orderly and equal manner, without accentuating any one organ or system of the body for premature senility? To this I know of no answer. However, I am convinced that with a greater interest and well planned research into the unexplored domains of aging, such as has been done by MacNider and the group who are members of the Club for Research on Ageing, great progress will be made.

It is generally accepted that involutional changes, which are characteristic of aging, begin at about 40 years of age, and though insidious in onset, later become more clearly manifest. At the same time there also begin those changes which result from degenerative diseases. Again referring to the records of patients who have been observed over a long number of years, there can be seen in many, the development of degenerative diseases which can be predicated upon the hereditary background or upon intoxications, methods and habits of living, and infections. This phase of geriatrics is one which should give physicians concern, since the problem in this instance is not to seek the prolongation of life so much as it is to see that the lives of those who are aging are made more effective by preventing, delaying or diminishing the progress of the degenerative state. What can clinicians do to improve this condition?

It is my belief that the first step in such a program for the successful practice of geriatrics should be that every person have a real health inventory, which is a much more comprehensive survey of the individual than the usual so-called health examination, which ordinarily is more or less perfunctorily done and when completed has detected only the rather obvious defects, missing entirely the beginning of changes which may lead to serious consequences. Such a comprehensive survey would determine what kind of an individual is being examined, as well as his physical status. Such an inventory, to be

all-inclusive, will require the aid of specialists; when once established and recorded it will be comparatively easy thereafter to detect developing variants. For such an inventory to accomplish the most good the patient should have explained to him all of the abnormal findings, particularly stressing the trends, and a safe and sane program outlined, which, if followed, will accomplish the desired objective. One of the discouraging features of such a program is that advice is wholeheartedly accepted and diligently followed for the time being only or but half-heartedly accepted and not followed at all. How often has the physician seen the fat, plethoric man or woman of 50 years come for examination and advice. After a careful history, physical examination, psychological interview and laboratory procedures, there is detected an overweight of 40 or 50 pounds, visible arterial changes in the retinal vessels, and blood pressure slightly elevated. A history is elicited of the excessive use of tobacco, working long hours, eating rapidly and considerably, little diversion, a constant drive, always being in a hurry, struggling, worrying and anxiety. The physician spends hours of time explaining to the patient just what is happening to his body or to his machine. All for what? The patient apparently is convinced and for the next five or six months follows advice; he loses weight, his appetite is curbed, he exercises, gets diversion and leads a life of moderation. However, unless followed he will soon revert to his old habits and tricks, and in another year will come with the story that he is feeling fine but that he is getting nervous, can't sleep at night, is restless, impatient, takes two or three drinks at night to relieve that tired feeling. Why is it this man or woman has not continued to follow the advice previously given? Patients are, after all, human beings, and perhaps the fault is not wholly theirs. The physician perhaps deserves criticism because he has not sufficiently or effectively impressed upon the patient the importance of preventive measures, and since there is no compulsion for the patient to follow the advice given, the hope to be of lasting help is to adopt methods similar to those used by pediatricians and dentists by calling patients in at intervals for an interview or check up. In this way the patient is conscious of a friendly interest in his welfare, and is made to realize that his physician is interested in preventing the development of disability and disease, the success of which will depend on the patient's willingness to cooperate in a health program.

More study, research and clinical observation should be made over a long period of time on the diseases commonly encountered in those who are aging. The hope of discovering some etiologic factor involved in the production of these diseases will increase with such effort. About some of the diseases of age a great deal is known, about others very little, and about all, very little from the standpoint of prevention.

I apologize for not being able to present a specific program or to add something new to the problem of aging. If I have been successful in emphasizing the importance of geriatrics as a division of the medical sciences in which there is a great opportunity for the medical profession to bring to those who are aging greater usefulness, happiness, and freedom from disabling and crippling diseases, the object of this rather scattered paper will have been accomplished.

Summary

Though life expectancy has been increased from 47 years in 1900 to 63 years in 1940, little has been done to meet the problems which the aging process presents, and little is known of the causes of degenerative changes. Heredity seems to determine to a greater extent than any other factor how well a person stands aging. Nutrition is probably a vital factor also, and the endocrine glands likewise affect the aging process. The first step in a program to pre-

vent or diminish the progress of degeneration should be a complete health inventory of older persons, with the results and trends explained to the patient and the importance of preventive measures impressed upon him.

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Splenectomy for Patients Past Sixty

GEORGE M. CURTIS AND DAVID MOVITZ

AMONG 14 PATIENTS PAST 60 YEARS OF AGE FOR WHOM A SPLENECTOMY WAS ACCOMPLISHED, THERE WERE 2 HOSPITAL DEATHS, A MORTALITY RATE OF 14 PER CENT. ALTHOUGH DISEASES REQUIRING SPLENECTOMY ARE NOT PECULIAR TO OLD AGE, CONSIDERATION OF SPLENECTOMY IN OLDER PATIENTS WILL BECOME MORE FREQUENT BECAUSE OF THE INCREASING NUMBER OF OLD PEOPLE. IT WAS FOUND THAT SPLENECTOMY WAS WORTHWHILE FOR THOSE WHO SURVIVED THE OPERATION BECAUSE THE PATIENTS WERE IMPROVED OR RECOVERED FROM THEIR SPLENIC DISEASE. THEIR EXPECTED LENGTH OF LIFE SUFFERED LITTLE OR NO INTERFERENCE. NO PATIENT IN THE ENTIRE GROUP SUCCUMBED TO THE SPLENECTOMY BECAUSE OF SENESCENCE.

IN A series of more than 200 consecutive splenectomies at the Ohio State University Hospital, there have been 14, or 7 per cent, performed on patients past 60. It has been our impression that these older patients have recovered fully as well as the younger ones, following removal of the spleen. On the other hand, clinical impressions, particularly those gained from the treatment of a number of patients, sometimes may be modified when existing records are carefully analyzed and summarized. As a consequence we have reviewed the findings on the older patients on whom splenectomies were performed, and at this time are reporting our principal conclusions.

Splenectomy at any age tasks the combined efforts of the anesthetist, the hematologist and the surgeon. The erythrocytes with their oxygen-carrying hemoglobin, the platelets necessary for the proper clotting of blood, the leukocytes involved in the processes of immunity, as well as vital hepatic functions may become inherently defective in diseases requiring splenectomy. In our entire series, a mortality rate of less than 10 per cent was experienced. In an even larger series an 11 per cent mortality was reported (1).

In 29 patients over 60, comprising 3.6 per cent of 776 splenectomies at the Mayo Clinic, the mortality rate was 20 per cent. In patients up to 39 years, a 5 to 8 per cent mortality was noted, but above that age there occurred a progressive rise to 20 per cent in those 60 years of age and older (2). The mortality rate of the similar aged group here reviewed was 14 per cent. This, nevertheless, does not contraindicate needed surgery in the aged. The urologists have pointed the way. A number of papers concerning surgery in the aged (3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13) as well as reports of specific surgery have appeared (14, 15, 16, 17).

The increasing proportion of aged people as well as a wider application of splenectomy for various hematologic disorders will result in the consideration of more elderly patients. Since 1850 the percentage of people between 50 and 64 years of age and also of those over 65 has doubled. This has resulted from two simultaneous factors, increasing longevity and a decreasing birth rate (18).

Pathologic states of the spleen requiring splenectomy are not peculiar to senescence, as are certain urologic and cardiovascular disorders, cataracts, fractured femurs, carcinoma, etc., since the spleen, as well as accessory spleens, partakes of the general involution characteristic of senescence. After the age of 65 the spleen weight diminishes progressively. Moreover, the ratio of spleen weight to body weight decreases from the time of birth onward, although the absolute maximum weight of the spleen is reached at 26 years (19). The accessory spleens also atrophy and involute, beginning as early as infancy (20). Thus there

Dr. George Morris Curtis, chairman of the Department of Surgical Research at the Ohio State University, received his Ph.D. in anatomy from the University of Michigan in 1914 and his M.D. from Rush Medical College in Chicago, in 1920. He was formerly professor of anatomy at Vanderbilt University, and later professor of surgery at the University of Chicago. His published work has included studies in anatomy, the physiology of the thyroid gland, iodine in nutrition, the metabolism of calcium, splenectomy, and in the field of thoracic surgery.

Dr. David Movitz is a graduate of the University of Kansas, receiving his M.D. degree there in 1936. He has been in general practice in Kansas City and has worked in the Department of Surgical Research at the Ohio State University. His chief fields of interest have been in splenic disease and particularly in the accessory spleen.

This investigation was aided by a grant from the Comly Fund for Research of the Ohio State University.

results a decreased incidence of accessory spleens in the aged (25). In patients with splenic hematologic disease, accessory spleens are found in 50 per cent of those in the first decade of life but in only 18 per cent of those in the seventh decade (25).

The dramatic results achieved for congenital hemolytic icterus or primary thrombocytopenic purpura clearly indicate splenectomy, even in the aged and even in the severer phases of these disorders (21). Splenectomy for certain variations within the Banti syndrome, such as primary splenic neutropenia (22) or pansplenic hematocytopenia (23), yields results which are clearly defined though not as dramatic, and is thus also indicated in the aged. That splenectomy usually benefits Banti's syndrome is shown in a series of 226 splenectomies for splenic anemia reported by Pemberton (1). Although 12.8 per cent died in the hospital, 55.1 per cent lived five years or more, 43.2 per cent survived ten years, and 22 per cent survived twenty years.

Splenectomy is apparently beneficial for certain selected patients with lymphatic leukemia in whom hemolysis or thrombocytolysis by the spleen has become excessive. The lengthening of life resulting from splenectomy in these patients has been variable but definite (23). Additional reason for splenectomy in the aged will usually be gained by a consideration of the additional life expectation at a given age (table 1).

TABLE 1.* EXPECTATION OF LIFE

Average Number of Years Lived After Indicated Age (1929–1931)

Age	White Male	White Female
60	14.73	16.05
61	14.12	15.38
62	13.52	14.72
63	12.93	14.07
64	12.35	13.44
65	11.79	12.83
66	11.25	12.23
67	10.72	11.64
68	10.20	11.07
69	9.70	10.52
70	9.22	9.98
71	8.75	9.46
72	8.29	8.96

* From Dublin and Lotka (18).

Surgery in the aged is based on the principles fundamental to all surgery. However, these principles must be more rigidly observed because of the various abnormalities and decreased system reserves of senescence. Age itself, however, is no rigid criterion of the degree of degeneration of the various tissues or of other changes. Many an individual of 65 is in better physical state than one of 50. A critical appraisal of the various systems and factors to be reckoned with must be made. Many factors affect the operative risk. In addition to those factors inherent in the primary disease requiring splenectomy, the cardiovascular and renal systems, hepatic functions, the respiratory tract, the metabolic systems including thyroid and pancreatic influence, the presence of focal infections, and the history of infectious diseases should be carefully evaluated. The body configuration, family longevity, nutritional status,

mental state, occupation, and mode of living may each be significant.

The age, sex, primary disease, and date of splenectomy, together with the general result obtained in 14 patients, form the basis for this report (table 2). Six patients were male and 8, female; the youngest was 60 years of age and the oldest, 71. Thirteen patients had splenic disease. Three patients were splenectomized for primary thrombocytopenic purpura, 2 for Banti's splenomegaly, 2 for thrombocytopenia secondary to lymphatic leukemia, 2 for primary splenic neutropenia, and 1 each for pansplenic hematocytopenia, congenital hemolytic icterus, acquired hemolytic icterus, and moniliasis of the spleen. In one patient removal of the spleen was incidental to an esophageal and gastric resection performed because of an esophageal carcinoma.

TABLE 2. SPLENECTOMY FOR PATIENTS OF 60 YEARS AND OLDER

No.	Age	Sex	Disease	Date Splenectomy	Result
1	60	F	Banti's Syndrome	1-10-35	Improved
2	61	F	Primary Thrombocytopenic Purpura	6-30-36	Recovered
3	66	M	Primary Thrombocytopenic Purpura	11- 3-38	Recovered
4	68	F	Primary Splenic Neutropenia	11-28-38	Recovered
5	63	M	Acquired Hemolytic Icterus	7-13-38	Improved
6	61	M	Moniliasis of Spleen	11-30-39	Died
7	62	F	Congenital Hemolytic Icterus	1-31-43	Recovered
8	69	M	Lymphatic Leukemia with Secondary Thrombocytopenia	9- 3-43	Improved
9	66	F	Pansplenic Hematocytopenia	11-18-43	Improved
10	65	F	Banti's Syndrome	3- 6-44	Improved
11	63	M	Lymphatic Leukemia with Secondary Thrombocytopenia	5-17-44	Died
12	71	F	Primary Splenic Neutropenia	10- 9-44	Improved
13	64	F	Primary Thrombocytopenic Purpura	6-26-45	Recovered
14	63	M	Esophageal Carcinoma (esophageal and gastric resection)	8-14-45	Improved

The hematologic studies were in most instances made by Dr. Charles A. Doan or Dr. Bruce K. Wiseman. Coincidental diseases, abnormalities, and senescent changes were evaluated so that such additional hazards might be dealt with suitably before splenectomy. Except for the hemolytic anemias, most anemias may be partially corrected by whole blood transfusions, using fresh blood if the platelets are also deficient. Thewlis states that preoperative hemoglobin levels should be 65 per cent or over (24). Splenectomy, however, is often undertaken despite severe anemia. Massage of the spleen, together with the use of adrenalin previous to the actual splenectomy, will nearly always increase the circulating erythrocytes and hemoglobin. Preoperative anemia may even offer added indication for operation in diseases requiring splenectomy.

Liver function deficiencies are usually treated with meat-free, high protein, high carbohydrate diets supplemented by vitamins (B complex, C and D), liver extract, and oral and intravenous glucose. This regimen is usually followed even though liver deficiency is not demonstrated by the ordinary tests. For prothrombin deficiency, vitamin K is administered daily. The patient with cardiac decompensation is digitalized and treated for other existing deficiencies. Renal deficiencies and respiratory tract diseases are suitably managed. During this time the patient becomes accustomed to the hospital, its attendants, and the modified routine, a factor of great importance to the aged.

General anesthesia is usual. Sodium pentothal for induction and intravenous curare for deeper relaxation supplementing inhalation agents are recent additions.

Cyclopropane is administered, providing no adrenalin is to be used. If the use of adrenalin is planned (to act in contracting the spleen), nitrous oxide instead of cyclopropane is employed. High proportions of oxygen are advantageous because of the frequent anemia. Occasionally anesthesia is begun with the local infiltration of novocain. Gastric distention preceding surgery is relieved by gastric suction, since the distention would greatly hinder exposure of the spleen.

The technique of splenectomy varies with the length of the splenorenal ligament and with the degree or absence of adhesions. A left paramedian incision is used. Splenectomy, type 1, may be referred to as the technique employed when a splenorenal ligament of sufficient length is present together with an absence of adhesions. In this the application of only one set of clamps is necessary. In type 2 the spleen is luxated out through the incision. This is permitted by the length of the splenorenal ligament. Adhesions present posteriorly and laterally must often be freed. Multiple clamps are then applied in the management of the pedicle. Type 3 is usually more difficult because of extensive adhesions of the spleen to adjacent structures. When these adhesions are few, not too firm, and predominantly avascular, they may be readily separated, and thus a type 3 splenectomy is converted to the less difficult type 2.

The degree of perisplenitis giving rise to adhesions varies with the causative disease. Thus, aside from the length of the splenorenal ligament, the type and ease of splenectomy varies with the character of the disease. Splenectomy, type 1 is usually done for the smaller spleen of primary thrombocytopenic purpura. Type 2 is usually employed for the removal of the spleen in congenital hemolytic icterus and occasionally for early forms of Banti's syndrome and its subdivisions, such as primary splenic neutropenia and pansplenic hematocytopenia. Type 3 is necessary occasionally. In this series of 14 splenectomies, type 3 was required for the patient with moniliasis of the spleen and for the patient with acquired hemolytic icterus. The kind of splenic disease thus becomes a factor of risk because of the additional hazards of type 3 splenectomies.

Immediately following removal of the major spleen for congenital hemolytic icterus or for primary thrombocytopenic purpura, it is essential to search for and remove any accessory spleens which may be present, lest they remain to cause recurrence of such disease (25, 26). Whether overlooked accessory spleens can cause recurrence of other splenic diseases, such as primary splenic neutropenia or pansplenic hematocytopenia, has not as yet been shown, but accessory splenectomy should not be a matter of chance. Removal of all splenic tissue is indicated. Few elderly patients have accessory spleens, however. Of those patients over 60, only 18 per cent with splenic disease were found to have accessory spleens (25). To avoid overlooking any, the following regions are searched in order: hilus, pedicle, omentum, retroperitoneal region surrounding the tail of the pancreas, splenocolic ligament, mesentery of the bowel, and, in women, the left adnexa. Most accessory spleens will be found at the hilus (25). Furthermore, remaining splenic tissue torn or cut from the major spleen may give rise to implants on the peritoneum, muscle, or subcutaneous tissue. This results in splenosis. Although it is not certain, these implants may theoretically result in recurrence of the primary splenic disease. Thus the incision should be protected if loose bits of splenic tissue occur. Injury to the spleen, which may be unavoidable when the adhesions are severe, is undesirable.

Postoperatively gastric suction is started, particularly to prevent gastric distention. Dilatation of the stomach might displace the ligatures from the gastrosplenic omental stump or even from the main pedicle stumps. In addition, gastric suction helps to keep the patient more comfortable by preventing nausea and permitting the drinking of fluids.

Of the 13 patients past 60 on whom

splenectomy was performed for splenic disease, 2 died in the hospital. The remaining 11 were improved, or recovered from their primary disease. Preoperative evaluation revealed multiple senescent changes or diseases in each patient. In addition to damage to the liver, which is often integrally associated with splenic disease, there occurred cardiac disease, hypertension, renal disease, pulmonary affections, and arthritis, all of which are more or less incident to senescence. Other abnormalities found were syphilis, disturbed nutritional states with emaciation or obesity, incisional hernia, and elevated basal metabolic rates.

Preoperatively 7 patients had enlarged hearts, usually associated with left axis deviation. One of these (no. 4—see table 2) also showed electrocardiographic evidence of myocardial damage. This patient was the only one decompensated, and was digitalized two days preoperatively. Postoperatively, 3 of the 7 developed cardiac decompensation—the patient that had been digitalized (no. 4) and another (no. 1), in the early postoperative days, and the third (no. 2) on the thirteenth postoperative day. All responded promptly to digitalis.

Two patients without preoperative evidence of cardiac abnormality (nos. 5 and 10) developed cardiac decompensation postoperatively. Patient no. 10 had been treated with forced fluids for a urinary infection. This patient also presented a positive luetic serology, emaciation, anemia and a mild ascites. Patient no. 5 had an associated hypoproteinemia. Both responded to digitalis and the administration of whole blood. One patient presented a diastolic hypertension and another a mild systolic hypertension. Thus, 9 of 13 patients in this series, or 69 per cent, had an associated cardiovascular disease. None succumbed postoperatively, however, to the effects of this abnormality.

Six patients presented laboratory evidence of a damaged liver preoperatively, 1 with primary thrombocytopenic purpura (no. 13), 1 with Banti's splenomegaly (no. 10), 2 with primary splenic neutropenia (nos. 4 and 12), 1 with pansplenic hematocytopenia (no. 9), and 1 with congenital hemolytic icterus (no. 7), who had had a cholecystectomy several years previously. At operation, the liver was enlarged or otherwise abnormal in the patient with splenic neutropenia (no. 12), in the patient with pansplenic hematocytopenia (no. 9), hippuric acid values being 2.7 gm. in both; and in the patient with lymphatic leukemia (no. 11), in whom the liver showed gross evidence of infiltration. A mild ascites was observed in the 2 patients with Banti's syndrome (nos. 1 and 10), and in the patient with pansplenic hematocytopenia (no. 9). Nos. 9 and 10 presented hippuric acid deficiency, 2.3 and 2.7 gm. respectively. No patient in the series developed definite signs of liver deficiency postoperatively (28). Preoperatively all were treated for liver damage whether decreased liver function was demonstrated or not.

Of the 6 patients with mildly decreased renal function, none developed renal insufficiency postoperatively although 3 had associated decreased hippuric acid values. A seventh (no. 10) revealed urinary retention on the day of operation. Although this condition required but one catheterization, the patient developed an Escherichia coli pyelonephritis, which responded but slowly to sulfathiazole and forced fluids.

Four patients presented lung abnormalities. One (no. 3) showed greatly increased bronchovascular markings by x-ray, another (no. 12), an emphysematous chest. A third (no. 7) had chronic bronchitis. The fourth (no. 6) had rales, dense fibrosis, and a suggestive cavitation in the apex of the left lung. This patient died shortly after operation from intraperitoneal hemorrhage. The patient with congenital hemolytic icterus suffered two mild episodes of pulmonary embolus, one on the first postoperative day and the second on the seventh postoperative day.

The patient with congenital hemolytic icterus also developed a phlebothrombosis which became apparent on the fifteenth postoperative day. Excessive thrombocytes are considered to be a predisposing factor to thrombosis subsequent to splenectomy.

One patient (no. 9) left the hospital with a platelet level above two million, and 5, with platelet levels above one million (nos. 1, 3, 5, 10, 12), including the patient (no. 3) who originally had primary thrombocytopenic purpura. The postoperative level of platelets in the patient developing clinical thrombosis (no. 7) was 1,540,000. This patient also had the highest preoperative level, 620,000 per cubic millimeter.

Other pathologic findings observed preoperatively and which apparently had no untoward effect on convalescence were: paralysis of the lower extremities in 1 patient (no. 2), hypertrophic arthritis in 4 (nos. 3, 5, 12, 13), emaciation in 4 (nos. 4, 5, 6, 10), moderate obesity in 3 (nos. 1, 9, 12), positive luetic serology in 1 (no. 10), a nodular goiter in 1 (no. 1), an incisional postcholecystectomy hernia in 1 (no. 7), and a nonvisualizing gallbladder in another (no. 5).

The elevated basal metabolic rates in 5 patients, ranging from 15 to 30 per cent, resulted in no apparent complications.

Three patients (nos. 3, 4, 9) developed wound infections. A small abscess noted on the twelfth day in one patient (no. 3) healed rapidly after drainage. A Staphylococcus albus infection in patient no. 4 became evident on the tenth postoperative day, resulting in separation of the skin edges. Healing occurred after several weeks. The third patient (no. 9) developed a hemolytic Staphylococcus aureus abscess, which became apparent on the eighteenth day. She subsequently required a secondary repair.

Two patients (nos. 6 and 11) died postoperatively, both from intra-abdominal hemorrhage. In patient no. 6 the spleen, infected with moniliasis, was adherent and difficult to free. It was torn at its upper pole where the adhesions to the diaphragm were dense. Death resulted in fifteen hours. The other death resulted from hemorrhage continuing after splenectomy for lymphatic leukemia because of the persistent thrombocytopenia.

Since hospital discharge, 2 of the 12 patients discharged have died. The patient with acquired hemolytic icterus died one year later from an empyema secondary to a traumatic fractured rib. Before death, however, there was still diminished evidence of hemolysis. The patient with primary thrombocytopenic purpura died two and a half years later from cerebral hemorrhage. There had been no recurrence of the purpuric bleeding. At the time of splenectomy this patient had arteriosclerosis, an enlarged heart, decreased renal function, and extensive neuropathy.

Two patients with primary thrombocytopenic purpura were doing well two and a half to three years later. The two patients with Banti's splenomegaly, one and a half to two years later, were experiencing mild symptoms of associated liver cirrhosis. The patient with thrombocytopenia secondary to lymphatic leukemia was doing well, two years later, the platelets being maintained at about 813,000.

The patient with congenital hemolytic icterus was improved six months subsequent to splenectomy. However, this patient again suffered a mild thrombosis, this time in the opposite lower extremity. The associated platelet level was 1,340,000.

The 2 patients with primary splenic neutropenia are both doing well. Patient no. 4, seven years after splenectomy, revealed a leukocyte count of 9,350 and a platelet level of 577,000. The patient with pansplenic hematocytopenia, followed for two years, appeared in good health, with 4.4 million red cells and normal leukocytes and platelets.

Discussion

Two patients died in the hospital of postoperative hemorrhage. There were no operative deaths because of senescence, subsequent to splenectomy. After dismissal from the hospital one patient died, a year later, from an empyema secondary to a traumatic fractured rib, and another, two and a half years later, from arteriosclerotic cerebral hemorrhage. Significantly, the two deaths after hospital dismissal did not re-

sult from the disease which required splenectomy.

Postoperative hazards usually ascribed to splenectomy are: (1) the effects of associated liver damage, (2) hemorrhage, and (3) thrombosis and its effects. No patient in this series demonstrated recognized postoperative complications referable to liver damage; only moderate liver damage was present, however. Since liver damage is often associated with splenic disease, particularly with Banti's syndrome, and thus the more in the aged because of superimposed degeneration, the patients were routinely treated for liver damage even if it was not apparent. Of 53 splenectomies reported by Eliason and Johnson (28), 21 were for Banti's syndrome. Seven of the 21 showed evidence of severe liver damage, and 6 of these died in the hospital. Two additional patients, in whom severe liver damage was discovered later, died at the time of operation. This accounted for all the deaths, though only 4 were termed "liver deaths" specifically.

Postoperative splenic and portal vein thrombosis is reported a frequent cause of death following splenectomy. Thrombosis evident clinically in one lower extremity occurred in 1 patient in our series. Of 28 deaths in Pemberton's series (1), 8 were the result of splenic and portal vein thrombosis, i.e., 29 per cent of the postoperative deaths. This complication subsequent to splenectomy has been frequently recorded (29, 30, 31, 32, 33, 34, 1, 2). It apparently results from two factors: (1) the postsplenectomy rise of platelets to abnormally high levels, particularly in the thrombocythemic group of Rosenthal (29), and (2) the slowing of the splenic and consequently the portal circulation as a result of the splenectomy. Approximately 20 per cent of the blood volume flowing through the portal vein is eliminated by splenectomy. Heparin has been suggested as a preventive (32), to be used in those patients with high postoperative platelet levels.

Hemorrhage results from one or more of three factors peculiar to surgery of the spleen: (1) technical operative difficulties, (2) prothrombin deficiency resulting because of liver damage, and (3) thrombocytopenia. Both of the deaths in our series resulted from postoperative hemorrhage, primarily from the operative area, one because of severe adhesions and mild thrombocytopenia, and the other because of lymphatic leukemia with a severe thrombocytopenia. Postoperative hemorrhages from the splenic pedicle, from within and without the stomach, and from adjacent areas have been reported (31, 32).

Degenerative changes, such as the abnormal heart, decreased renal function, lowered respiratory reserve, and arteriosclerosis, unless severe usually offer no insurmountable obstacles to splenectomy.

Heart disease occurs in the aged so frequently that surgical intervention must often be considered even in the presence of cardiac abnormalities. In Levine's study (35) an operative mortality of 12 per cent was noted in 494 major operations on 414 patients with organic heart disease. By excluding those in whom death would have occurred because of the cardiac condition irrespective of operation, an "unexpected" mortality rate of only 6.3 per cent occurred. Analysis of the unexpected deaths according to the type of heart disease revealed only a 2.1 per cent mortality in those with valvular heart disease (147 operations), and 4.9 per cent in those with nonvalvular heart disease such as hypertension and chronic myocarditis (167 operations). That surgical procedure is hazardous in the presence of congestive heart failure is indicated by the operative mortality of 14 per cent in 50 operations on patients with congestive failure. Patients with organic heart disease who are well compensated withstand major surgical operations satisfactorily.

After 41 operations on patients with an associated angina pectoris, 7.7 per cent died. Of patients with associated coronary thrombosis, after 20 operations 40 per cent died. This high mortality rate was attributed to operations in the midst of an acute coronary thrombosis and to opera-

tions which could have been delayed. Out of 108 patients with permanent auricular fibrillation, only 3 deaths occurred, a 3 per cent mortality rate; of patients with syphilitic aortitis 1 death in 13 operations was reported. In 6 patients with paroxysmal tachycardia, 3 of whom had an attack during surgery, no deaths occurred.

Levine further found the mortality rate to differ significantly depending on whether nephritis was superimposed. In patients with superimposed nephritis the rate was 14.8 per cent, and in those without nephritis, 4.9 per cent. No significant effect of hypertension on mortality was noted.

Arteriosclerosis apparently reduces the reactivity of the circulatory system to sudden volume changes (36). Therefore, replacement of whole blood should be prompt and adequate. The fluid and mineral balance should be carefully maintained to protect the kidneys and heart rather than to burden them. Prevention of pulmonary stasis along with good nursing care will also aid in the aged patient's recovery.

Summary

Fourteen splenectomies in patients past 60, representing 7 per cent of 200 consecutive splenectomies at the Ohio State University Hospital, are reviewed. Two hospital deaths, or 14 per cent, occurred in the aged group, as compared to 10 per cent for all 200 cases. The consideration of splenectomy in the aged will be more frequent because of the increasing number of older people. The diseases requiring splenectomy are not peculiar to old age. Splenic tissue, however, partakes of senescent involution.

The good results obtained by splenectomy for congenital hemolytic icterus, primary thrombocytopenic purpura, Banti's syndrome and some of its clarified complexes indicate the procedure for these diseases in the aged. It also appears probable that splenectomy is indicated for excessive splenic thrombocytolysis or hemolysis in lymphatic leukemia.

The hazards of splenectomy and those resulting from senescence are analyzed. The technique of splenectomy is more hazardous in those splenic diseases which result in greater adhesions. The removal of accessory spleens, to prevent recurrence of the original disease is emphasized.

Postoperative gastric distention should be carefully avoided. Liver damage was found in 60 per cent of the patients on whom splenectomy was performed, associated heart disease in 69 per cent, and decreased renal function in 46 per cent. No patient succumbed from the effects of any of these pathologic conditions. Other abnormalities noted preoperatively were: abnormalities of the lung in 4 patients, hypertrophic arthritis in 4, emaciation in 4, moderate obesity in 3, elevated basal metabolic rates in 5, paralysis of the lower extremities in 1, nodular goiter in 1, nonvisualizing gallbladder in 1, and an incisional hernia (postcholecystectomy) in 1.

Postoperatively, 5 patients developed mild cardiac decompensation which responded readily to digitalis. One developed an Escherichia coli pyelonephritis which became evident by the tenth postoperative day. The patient splenectomized for congenital hemolytic icterus suffered two mild episodes of pulmonary embolus, one on the first and the other on the seventh postoperative day. Also, on the fifteenth day this patient showed evident thrombosis in the left lower extremity. This patient had the highest preoperative platelet level, 620,000. Three patients developed wound infections.

Two patients died, both from postoperative hemorrhage—one, because the bleeding, caused by a severe thrombocytopenia associated with lymphatic leukemia, persisted after splenectomy, and the other, as a result of the trauma in freeing unusually dense adhesions around a spleen infected with moniliasis. In the follow-up period thus far, 2 patients have died, one from arteriosclerotic cerebral hemorrhage, and the other from complications secondary to trauma.

This study reveals (1) that with many senescent changes, though none severe, no

patient of the elderly group succumbed to the relatively hazardous operation of splenectomy because of senescence; (2) that the two deaths occurring shortly after splenectomy were the result of hemorrhage, because of technical difficulties in one case and because of the primary disease in the other; (3) that 2 of the remaining 12 patients have since died, one a year later as the result of an accident, and the second, two and a half years later as the result of old age; and (4) that splenectomy for those who survived the operative procedure has been worthwhile from two points of view: The patients have improved or recovered from the splenic disease, and, secondly, their expected length of life has suffered little or no interference from the previous splenic disease.

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Selective Placement of Older Workers

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THE WAR BROUGHT ABOUT A CHANGE WHICH SOCIAL PLANNERS HAVE BEEN TRYING TO ACHIEVE FOR MANY YEARS—THE EMPLOYMENT OF OLDER PERSONS IN INDUSTRY. STUDIES HAVE SHOWN THAT OLDER PEOPLE MAKE SATISFACTORY WORKERS WHEN PROPERLY PLACED IN JOBS. FORMER UNSCIENTIFIC PROCEDURES FOR JOB PLACEMENT ARE BEING REPLACED BY MORE SCIENTIFIC ONES BASED ON ANALYSES OF THE PHYSICAL AND ENVIRONMENTAL DEMANDS OF EACH JOB AND THE PHYSICAL CAPACITIES OF THE WORKER. THUS SPECIFIC CAPACITIES OF A WORKER CAN BE MATCHED WITH THE SPECIFIC DEMANDS OF A JOB. WHEN PROPERLY PLACED, THE AGED CAN PROVE THEIR WORTH AS COMPETENT AND EFFICIENT WORKERS AND CAN MAKE A PLACE FOR THEMSELVES IN INDUSTRY.

THE proper placement at work of older workers requires, as in the case of any worker irrespective of age, the evaluation of experience, skills, and physical capacities in relation to the demands of the job. Here at the Permanente Foundation Hospital the staff has been particularly interested in the physical capacities of workers, leaving the evaluation of other characteristics to the employment agency representative, the personnel man, or the industrial psychologist.

Heretofore in the selective placement of workers, the industrial physician has been accustomed to classify workers, actually or by inference, into about four groups: (1) fit for any work, (2) fit for moderate work, (3) fit for light or sedentary work, and (4) fit for no work (1). It was then the function of the placement officer to interpret these broad classifications when attempting to place the worker on a specific job. Just what is meant by "moderate work" or "light work" is a matter of individual interpretation. There is little scientific justification for such classification.

The first significant attempt to break away from unscientific procedures came when research workers in the field of job placement began to analyze the physical and environmental demands of particular jobs. With such information available concerning jobs, it was natural to inquire whether they could be performed by individuals with specific physical defects, as, for example, lack of one arm or one leg or high blood pressure. Lists were then prepared of jobs in an industry or group of industries performable by individuals with specific handicaps. Such lists have been the basis of a number of placement programs.

However, there are inherent weaknesses in this approach to the problem of job placement. Specific physical defects are not invariably easy to classify. Take, for example, heart disease, which can be broken down into many categories.

A list of jobs performable by individuals with each type of heart disease would have to be prepared, for it is obvious that a comprehensive list of jobs performable by individuals having heart disease in general, has little practical value. A job for a young worker with rheumatic heart disease would not suit an aged man recovering from coronary thrombosis.

Furthermore, it is sociologically undesirable to single out individuals with physical defects. This procedure tends to segregate handicapped persons and increase the difficulty attendant upon placing them in industry. Theoretically, there is no reason why a placement program cannot be adapted to the placement of nonhandicapped workers as well as handicapped. So the conclusion must be drawn that in the final analysis the proper placement of a worker on a job is the placement which matches the specific capacities of a worker with the specific demands of a job.

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New Developments

These were some of the considerations that led the staff at the Permanente Foundation Hospital, with the assistance of Bert Hanman, a job analyst and expert on placement, to investigate whether the same terminology could not be used to analyze the physical characteristics of both people and jobs. Two subdivisions were to be considered: the job itself and the job's environment. If this type of analysis could be effected, the problem of placement would be appreciably simplified. Further study of the question led to the conclusions that this could actually be accomplished (1, 2, 3).

Keeping this objective in mind, the following list of twenty-five mechanical factors was prepared as a basis for analyzing both jobs and workers at the Kaiser shipyards:

Mechanical Factors

1. Lifting
2. Carrying
3. Handling
4. Pushing
5. Pulling
6. Climbing
7. Jumping
8. Running
9. Walking
10. Standing
11. Stooping
12. Crouching
13. Kneeling
14. Crawling
15. Twisting
16. Reclining
17. Sitting
18. Reaching
19. Fingering
20. Feeling
21. Talking
22. Hearing
23. Seeing
24. Color Vision
25. Depth Perception

Consider the item "lifting," for example. The job analyst can definitely determine how much lifting, if any, a specific job requires. The industrial physician can say whether or not an individual worker should be restricted in respect to lifting, and, if so, what maximum weight he should lift. Therefore, in respect to the lifting factor, the placement officer can say whether the worker is suited to the specific job. Similar treatment can be accorded the other twenty-four physical factors.

Likewise, the following list of twenty-five environmental factors was prepared as a basis for analyzing both jobs and workers at the Kaiser shipyards:

Environmental Factors

1. Inside
2. Outside
3. High Temperature
4. Low Temperature
5. Sudden Temperature Changes
6. High Humidity
7. Low Humidity
8. Toxic Conditions
9. Radiant Energy
10. Moving Objects
11. Mechanical Hazards
12. Electrical Hazards
13. Exposure to Burns
14. Explosives
15. Vibration
16. Noise
17. High Places
18. Cramped Quarters
19. Wet Quarters
20. Working With Others
21. Working Around Others
22. Working Alone
23. Day Shift
24. Swing Shift
25. Graveyard Shift

In respect to the item, "inside," the job analyst can readily determine whether the job under analysis is inside or not, and the industrial physician can say whether the worker under consideration may work inside or not. In respect to this factor, therefore, the placement officer can be given information which will enable him to place workers effectively. Similar considerations apply to the other twenty-four environmental factors.

Example of Placement

For example, a man of 70 who has arteriosclerosis, chronic bronchitis, normal blood pressure, and corrected distant and near vision of 20/40 and Jaeger 2, respectively, in each eye, may be considered. His physical capacities might be as follows: May lift and carry, or push and pull, up to 25 pounds six times per hour, one hour a day. May walk, stand, stoop, crouch, and kneel up to three hours. No climbing,

jumping, running. No outside work, exposure to sudden temperature changes, or work in wet quarters. Day shift only.

This worker could be used on many jobs. Specifically, the job of welder in the reclamation shop may be considered. The job's analysis is as follows: Stands and reaches forward into bin to grasp, lift, and carry steel strips weighing up to 10 pounds about 10 feet to work bench (one hour). Sits at bench 30 inches high and reaches forward to handle 1-pound electrode holder during welding process and to handle light wire brush and slag hammer while cleaning weld (seven hours). Stands, stoops, and reaches down to handle controls to adjust electric generator (one-half hour). Must be able to see 1/8 inch red tip at 12 inches. No talking or hearing required. Physical factors similar on day and swing shifts. Works day or swing shifts inside reclamation shop. Exposed to black-iron welding fumes, to rays from electric welding arcs, to sharp edges of materials, to uninsulated parts of electrode holder, and to hot metals and electric arcs. Environmental factors similar on day and swing shifts.

It will be seen that the septuagenarian under discussion could fill the job as far as every mechanical and environmental demand is concerned.

Because of a clause in the labor union agreement which barred preplacement examinations, the newly developed technique was used exclusively for transfer of a Kaiser shipyard worker from one job to another, although, of course, the technique would be as usable for preplacement. During the first eighteen months the program was in effect 10,000 physical capacities analyses were made out for all sorts of disabilities, many of them among older workers.

Surprisingly, the technique's greatest usefulness was in getting a disabled worker back to work sooner than would otherwise have been the case. Ordinarily, a physician might wait until a fractured arm or leg was completely healed and then return the man to his original job. But with the aid of the physical capacities analysis the doctor could very easily assign the injured worker to other temporary work, merely indicating for the man with a cast on his leg: "No climbing for six weeks." This recommendation might keep a partly recovered welder off the boats, but his services could be used in pipe or plate shop. This earlier return to work not only speeded shipbuilding, but prevented pay loss and was good for the worker's morale.

Placement of Cardiac Patients

The cardiologists took particular interest in placement, and used the procedure to advantage in heart cases, which were second in number only to orthopedic cases.

In general it might be said that until more is known concerning the relationship between clinical data and physical capacities, the physician's judgment is probably the best and only guide. However, the cardiologists attempted to develop certain criteria (4). For example, the physical examination, electrocardiogram, chest x-ray for heart size, and past history in respect to arduousness of work were all taken into account. Tabulation of criteria for guidance of staff physicians has been done for hypertensive heart disease, coronary arteriosclerotic heart disease, rheumatic heart disease, syphilitic aortic valvular disease and congenital heart disease. For coronary arteriosclerotic heart disease the criteria in table 1 would apply.

The placement of the first 84 cases of coronary thrombosis was analyzed (5), and it was found that of 56 patients who had returned to work, 30 had been working over a year, 19 of them on the same job, 11 on lighter work. Of the 19 back on the same work, 15 were doing manual labor. The cardiologists believed that patients recovering from coronary thrombosis had practically a 50–50 chance to return to hard, manual work. It could not be assumed, therefore, that serious heart disease invariably doomed a laborer to change of job. When it did, however, proper placement to prevent the ill effects which might result from a worker's exceeding his ca-

TABLE 1. WORK RECOMMENDATIONS FOR CARDIAC PATIENTS HAVING CORONARY ARTERIOSCLEROTIC HEART DISEASE

Therapeutic Classification*	Work Recommendations
Class A	
Class I.** No symptoms on ordinary activity or regardless of activity. No cardiac enlargement. (Patient may have recovered from myocardial infarction.) Must be prohibited from taking jobs in which sudden collapse would endanger others.	No restrictions
Class B	
Class II. Symptoms on ordinary activity, or at activity comparable to job. Rare attacks of angina. (Patient may have recovered from myocardial infarction.)	50 per cent of ordinary activity
Class C	
Class III. Symptoms on less than ordinary activity. Basal rales. Cardiac hypertrophy, moderate. Occasional attacks of angina, mild.	25 per cent of ordinary activity
Class D	
Class IV. Symptoms on less than ordinary activity. Frequent or moderately severe angina. Minimal signs of congestive failure. Digitalized.	Sedentary work
Class E	
Class V. Symptoms at rest. Signs of congestive failure in spite of digitalis. Severe angina, or angina at rest. Recent coronary occlusion (within three months).	No work

* The therapeutic classification (A, B, C, D, and E) follows that of the American Heart Association.

** Numerals represent the functional classification of the American Heart Association. (Nomenclature and Criteria for Diagnosis of Diseases of the Heart, New York Heart Association, New York.)

pacities could best be made by a carefully executed program.

Despite the fact that aged men could fill many jobs as far as their physical capacities were concerned, it was found that older men were not getting certain jobs. For example, they were frequently barred from welding. Like most persons in advanced years, these older people wore bifocal glasses with lenses divided for distant vision at the top, near vision below. The welding hood covered the lower part of the lense and made it practically impossible for them to work. The solution was found in grinding a correction for near vision into glass placed in a plastic plate which could be slipped into the welding hood itself.

REENGINEERING AND REHABILITATION

Such assistance to older workers illustrates the kind of planning that can be done to suit to the aged jobs for which they would not otherwise be fitted. If a machine operation requires too much pulling, the plant engineer might possibly rearrange or alter the length of levers to reduce the effort required. If a job requires too much stooping for a senescent, arthritic back, placing the work area nearer to the level of the worker's shoulders might help a great deal.

Where such job reengineering is not possible the older worker should be transferred to work he can do. For example, the same finger dexterity cannot be expected in a man of 80 that he possessed at 20.

There are, of course, workers, both old and young, who cannot earn a living because they have completely lost their previous skills through accident or illness or the passing of time. These persons should be trained for new work. An aged laborer

who can no longer work standing on his feet may earn a living at sedentary work.

Thus, an outgrowth of the selective placement program was the establishment of a rehabilitation service for incapacitated shipyard workers through the cooperation of the State Bureau of Vocational Rehabilitation. A representative of the bureau called at the hospital once a week to work with candidates for rehabilitation. When further study was needed, the candidate, as soon as he was ready, was referred to the bureau headquarters in Oakland or San Francisco (6).

The bureau required a full report on each candidate for rehabilitation, setting forth his physical capacities, diagnosis and prognosis. Since the staff physicians had considerable experience with the physical capacities analysis, the bureau waived the use of their regular report forms and instead the forms in use at the hospital were substituted.

In general, the experience, herein discussed, in the employment of older workers in the shipyards during the war supports the contention of students of the problem—namely, that aged persons can become satisfactory workers. Thewlis (7), for example, says: "There is no decline in earning power with advancing age. There are fewer industrial accidents with elderly workers, labor turnover is smaller. Output is often equal to that of younger workers. In some cases the productivity is increased. Older workers are likely to be more stable, loyal, and responsible." It should be pointed out, however, that although with increasing age there is a tendency for reduction of the number of disabilities which one worker may suffer during a year, the number of days of disability per worker and the number of disabled workers per thousand tends to increase with age (8).

The war brought to pass automatically what social planners had been trying to achieve for many years through education or mutual agreement—the employment of older persons. I recall that back in 1939 through the efforts of an assemblyman, James J. Wardsworth, the clothing industry in upper New York State entered into an agreement to employ the same percentage of people over 40 as existed in the local population. Mr. Wardsworth wrote me recently that the war eliminated the need for this agreement because older people naturally found their way into industry.

Since the aged have proved their worth during the war it is hoped that the future will see a greater proportion of them kept in industry and properly placed on work they can do. When the aged are placed more efficiently, it can be expected that a good record will be further improved.

Summary

Older workers are satisfactory workers, especially when properly placed at work. Selective placement requires evaluation of the worker's experience, skills and physical capacities in relation to the demands of the job. A technique has been developed which physicians can use for analysis of physical capacities.

Job reengineering and rehabilitation also enter into the problem of placing the older worker on work for which he is physically suited. The war has opened the nation's eyes to the value of the older worker in industry, and this experience should be utilized in the postwar years ahead.

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The Effects of Androsterone, Oestradiol and Thyroid Hormone on the Artificial Premature "Climacteric" of Pure Gonadal Origin Produced by Ovariectomy in Rats

I. Effects on Weights of Organs

V. KORENCHEVSKY AND VERA E. JONES

FROM AN EARLY PERIOD OF LIFE AGING CAUSES A DECREASE IN RELATIVE WEIGHT IN MANY ORGANS OF THE RAT. DR. KORENCHEVSKY AND DR. JONES, EXPERIMENTING ON OVARIECTOMISED RATS, HAVE COME TO THE CONCLUSION THAT OVARIECTOMY HASTENS THIS PROCESS OF AGING. THEY HAVE ALSO STUDIED THE MODIFYING EFFECTS ON THE HYPOPLASIA OF ORGANS OF THREE HORMONES—THYROID, ANDROSTERONE, AND ESTRADIOL—GIVEN ALONE OR SIMULTANEOUSLY. THE EVIDENCE INDICATES THAT THE HYPOPLASIA CAN BE PREVENTED, AT LEAST FOR A CERTAIN PERIOD OF TIME, BY ADMINISTRATION OF ONE OR MORE OF THESE HORMONES, THYROID AND ESTRADIOL BEING PARTICULARLY EFFECTIVE.

HYPOPLASIA, resulting in atrophy of organs and tissues, is one of the most specific and important features of aging (Warthin, 83, Rolleston, 72, Korenchevsky, 46). Ovarian hypoplasia and hypofunction are the foremost factors in producing the climacteric. Therefore, from an experimental point of view, the conditions produced in the young or adult female organism by ovariectomy might be considered as an artificial, premature, and extreme "climacteric" of purely gonadal origin. Experimentation with this condition could be used as a method of gerontologic research since the artificial climacteric is isolated from the aging decay of other organs rather than complicated by it as is the natural climacteric. Research along similar lines on other endocrine glands involved in the process of senile atrophy and degeneration should help to elucidate the special role and features displayed by each gland in the process of aging.

Even if atrophic or degenerative changes in endocrine glands, and in particular in the gonads, are not primary but only secondary causes of aging, from the moment they appear they initiate pathologic conditions which indicate deficiency of specific glands. These pathologic changes are added to those produced by the primary causes of senility, and in this way a number of vicious circles are produced which complicate and speed up the process of aging. Therefore in the treatment of old age the various hormones may reasonably be expected to alleviate some senile features by breaking up one or more of these vicious circles.

In the case of senile hypoplasia and atrophy those hormones and natural compounds which produce an opposite, or hypertrophying, effect on the various organs and tissues may be of especial value. Previous results obtained by other authors and by us indicate that thyroid, androgenic hormones, and, under certain conditions, oestrogenic hormones possess such stimulating properties.

An investigation of the simultaneous effects of different hormones is important be-

Dr. V. Korenchevsky, a Russian by birth, was formerly professor of experimental pathology at the Imperial Medical Academy in Petrograd. He received his M.D. degree from Moscow University. In 1920 he emigrated to England, becoming a naturalized British citizen. He was senior research worker at the Lister Institute of Preventive Medicine in London. He was an initiator of and active in the foundation, in 1939, of the Club for Research on Ageing, with branches in Europe, the United States, and Argentina. Dr. Korenchevsky is now Hon. Secretary of the British branch. In 1945 he was appointed head of the Gerontological Research Unit at Oxford, establishment of which was made possible by a grant from Lord Nuffield. Hospitality has been extended to the Unit by Prof. A. C. Hardy and Prof. E. G. T. Liddell of the department of zoology and department of physiology at Oxford University. The subjects of research in which Dr. Korenchevsky is most interested include endocrinology, the study of vitamins, and gerontology.

Dr. Vera Evelyn Jones obtained her B.Sc. degree in zoology in 1941 and her Ph.D. degree in 1944 at Liverpool University. She has been a research worker at Liverpool University and at Reading University, National Institute for Research in Dairying. Since January, 1945 she has been with the Gerontological Research Unit at Oxford University. Her work has been chiefly with cancer research and gerontology.

Ciba, Ltd., in particular Dr. K. Mieschcr, supplied the hormones used in the experiments here reported on, and Parke, Davis, and Co., supplied the desiccated thyroid.

cause (1) in the organism all hormones are secreted simultaneously; (2) some hormones become effective or specific, or their unfavourable effects are neutralised, only when certain other hormones are present; and (3) unless there is definite evidence of a single deficiency, treatment with one hormone only might produce hyperhormonisation and therefore a dangerous upset in the balance of the hormones.

All these considerations explain the purpose of the experiments reported on in this paper—namely, to show the effects of simultaneous administration of three hypertrophying hormones (androsterone, oestradiol and thyroid hormone), all normally present in the female organism, on the premature artificial climacteric of purely ovarian origin, which is produced by removal of the gonads in female rats. Dehydroandrosterone, the second androgen naturally present in the female, has been deliberately omitted from this discussion, as its effects on female rats are similar to those of androsterone but are much weaker either alone or in combination with oestrogens (48, 54).

Obviously, detailed study of changes in the weight of organs is a direct and primary method for assaying the hypoplastic and atrophic changes of aging. Therefore in this paper, discussion of the investigation of these changes in the weight of organs precedes a detailed histologic study of the experiments made (see paper, page 336, this issue).

Technique

Two series of experiments on a total of 119 female rats, 11 normal and 108 ovariectomised, are described.

The arrangement of the experiments into various groups and the amounts of hormones given to each group are clear from tables 1 and 2. The rats were ovariectomised at the age of 21 to 24 days. Litter mates were distributed as evenly as possible among the different groups. At the end of the experiments the average age was 182 days in the first series of experiments and 152 days in the second. The duration of the experiments was 56 days in the first and 76 days in the second series. All animals were killed by bleeding.

The sex hormones were dissolved in sesame oil, and 0.2 cc. of the solution injected subcutaneously as a single dose. Control rats received 0.2 cc. of pure sesame oil. Desiccated thyroid was administered by pipette in the form of a sweetened emulsion, and thyroxine was injected subcutaneously.

All organs were weighed after fixation in Bouin's fixative. The dissected retroperitoneal fat and the fat attached to the sex

organs were weighed together and represent the "abdominal" fat listed in the tables.

In order to confirm the results obtained with oestrogens and androsterone, reference will be made to some previous experiments of a similar nature on 210 rats, the data on which (partly unpublished) have been recalculated per unit of "fat free" bodyweight and reexamined. The details of these previous experiments will be published later.

The hypoplasia that results from aging was studied in 162 normal and spayed rats, used as control animals, in previous experiments (also partly unpublished). These experiments are summarised in table 3.

Effects of Ovariectomy and of Hormones Administered Separately

There is an extensive literature on the effects of ovariectomy and on the effects of the hormones studied in our experiments. In order to avoid repetition and make the reading of the paper easier, and also to facilitate comparison of the results presented in this paper with the results of other workers, each part of the paper will be preceded by a review of the relevant literature—that is, literature concerned

Table 1. Effect of Androgenic, Oestrogenic and Thyroid Hormones, Administered Separately or Simultaneously, on Actual Weight of Organs

Weekly doses of hormones: Desiccated thyroid 105 mg. = "small dose"; Oestradiol B.B. 0.015 mg. injected for first 3 weeks only = "small dose". Oestradiol B.B. 0.09 mg. injected every week = "large dos "; Androsterone 4.5 mg.

Organs	Ovariectomised controls	Thyroid hormone (small dose)	Oestradiol B.B. (small dose)		Oestradiol B.B. (large dose)		Androsterone		
			Alone	+Thyroid (small dose)	Alone	+Thyroid (small dose)	Alone	+Thyroid (small dose)	+Thyroid and Oestradiol B.B. (small dose)
Uterus (mg.)	33	39	191	220	239	240	36	40	240
Vagina (mg.)	158	187	273	304	270	273	247	224	333
Preputial glands (mg.)	50	53	48	44	41	64	107	116	123
Adrenals (mg.)	58	63	55	84	80	91	49	52	77
Thyroid (mg.)	19	18	18	18	18	17	20	21	22
Hypophysis (mg.)	14.9	14.7	13.8	15.8	46.4	46.9	14.9	13.8	15.4
Thymus (mg.)	191	228	125	158	98	120	166	170	133
Liver (gm.)	7.61	7.94	5.97	7.27	8.38	9.00	8.51	9.44	8.21
Kidneys (gm.)	1.48	1.67	1.34	1.69	1.66	2.05	1.65	1.81	1.84
Spleen (mg.)	879	788	460	797	578	648	543	783	978
Heart (mg.)	810	953	783	907	783	943	901	1055	984
Abdominal fat (gm.)	13.2	12.4	12.0	9.8	9.9	8.3	16.1	15.7	17.0
Final body weight (gm.)	264	262	220	223	224	231	283	288	262
Number of rats in each group	8	10	5	5	4	5	6	6	7

with the hormones we have studied and with the effects of these hormones on female rats only, with a few unavoidable exceptions.

The actual weights of organs are given in tables 1 and 2, but mention will be made in the text as to whether or not the relative weights give the same results. Only those relative weights which are indispensable for confirmation of some of the conclusions made are given in table 4.

Statistical analysis of all results was made by Fisher's t-test for small samples. For statistical significance (P) of the changes obtained, the values of normal and experimental groups were compared with the group of control ovariectomised rats (unless otherwise stated).

The Effects of Ovariectomy.—Body weight was found by all authors to be greater in ovariectomised female rats than in control rats (35, 36, 81, 78, 71, 25, 28–30, 40, 59, 85, 82, 8). In previous experiments (47–52, 54, 56) and in the present investigation (see table 2) the body weight of spayed rats was also found heavier than in the control litter mates. The increase was on an average about 23 per cent with a

TABLE 2. EFFECT OF ANDROGENIC, OESTROGENIC AND THYROID HORMONES, ADMINISTERED SEPARATELY OR SIMULTANEOUSLY, ON ACTUAL WEIGHT OF ORGANS

Weekly doses of hormones: Dessicated thyroid 250 mg. +Thyroxine 0.8 mg. = "thyroid hormone large dose"; Oestradiol B.B. 0.015 mg. injected for first 3 weeks and 2 last weeks = "medium dose"; Oestradiol B.B. 0.09 mg. injected every week = "large dose"; Androsterone 4.5 mg.

Organs	Normal Controls	Ovariectomised Controls	Thyroid hormone (large dose)	Oestradiol B.B. (medium dose)		Oestradiol B.B. (large dose)		Androsterone		
				Alone	+ Thyroid horm. (large dose)	Alone	+ Thyroid horm. (large dose)	Alone	+ Thyroid horm. (large dose)	+ Thyroid horm. (large dose) +Oestradiol B.B. (medium dose)
Uterus (mg.)	419	31	31	241	279	313	403	33	33	314
Vagina (mg.)	304	164	175	289	324	297	348	214	216	370
Preputial glands (mg.)	80	58	67	51	59	56	62	137	170	183
Adrenals (mg.)	61	55	86	84	135	70	104	42	70	123
Thyroid (mg.)	15	14	14	16	15	17	17	15	16	17
Hypophysis (mg.)	15.3	15.4	14.2	19.8	19.8	38.7	33.5	15.2	14.7	18.7
Thymus (mg.)	206	295	357	172	182	131	109	258	211	159
Liver (gm.)	6.94	6.79	9.17	8.01	11.55	8.00	9.68	8.78	9.99	10.57
Kidneys (gm.)	1.51	1.44	2.12	1.60	2.54	1.55	2.17	1.65	2.18	2.60
Spleen (mg.)	603	815	988	698	1024	609	770	794	1190	948
Heart (mg.)	784	768	1123	813	1200	708	959	893	1162	1110
Abdominal fat (gm.)	11.6	6.5	1.5	7.1	1.7	7.2	2.6	11.4	2.2	2.6
Final body weight (gm.)	216	235	216	207	215	205	210	278	233	230
Number of rats in each group	11	7	7	6	6	4	4	6	6	6

range of from 8.8 per cent to 36 per cent in different experiments.

Body length likewise was stated to be greater after ovariectomy (81, 35, 36, 78, 40, 59, 28).

Obesity, according to all authors, is not a constant feature of ovariectomy as it occurs only in some animals or human beings. Therefore, summarizing his own results and those of other workers on the subject, Korenchevsky (44) suggested that gonadectomised animals or human beings be designated "fat" or "thin" castrates as the case might be.

In ovariectomised rats, fat deposition was found by some authors (71, 40, 8) to be unchanged, but was recorded by others (35, 81, 78) as increased.

In the previous experiments of Korenchevsky and his co-workers and in the experiments reported on in this paper, fat deposition, as judged by the actual weight of dissected abdominal fat, was definitely increased over the normal control rats in only one of the experiments. In other workers' experiments, some of which are summarized in table 3, fat deposition varied, but for the most part only small changes were observed. In one of the present experiments (table 2) fat deposition was decreased. Therefore, in the female rat as in other species, there are fat and thin castrates. That the uterus and vagina become atrophic after ovariectomy is a long established fact. In all previous experiments and also in the present experiments female pre-

TABLE 3. EFFECTS OF AGING ON RELATIVE WEIGHTS OF ABDOMINAL FAT AND ORGANS PER 200 GM. OF FAT-FREE BODY WEIGHT IN NORMAL (N) AND IN OVARIECTOMIZED (OV) FEMALE RATS

Age in Days	50–60		61–70		71–80		81–90		91–140		151–210	
Group of rats	N	OV	N	OV	N	OV	N	OV	N	OV	N	OV
Body weight (fat-free, gm.)	—	172	154	194	178	206	181	211	183	236	—	231
Abdominal Fat (gm.)	—	3.8	9.6	8.4	14.2	14.6	13.8	14.9	21.7	14.7	—	12.9
Ovaries (mg.)	—	—	96	—	82	—	84	—	82	—	—	—
Uterus (mg.)	—	34	421	34	399	36	427	34	416	31	—	31
Vagina (mg.)	—	122	287	133	285	135	263	125	284	144	—	157
Preput. gl. (mg.)	—	100	134	76	106	65	110	54	109	53	—	41
Adrenals (mg.)	—	87.9	78.6	78.7	79.7	80.9	81.2	66.3	84.8	63.6	—	41.4
Thyroid (mg.)	—	18.0	20.9	19.1	19.8	21.2	22.9	18.4	26.8	18.7	—	14.7
Hypophysis (mg.)	—	12.9	16.8	12.7	15.6	12.5	14.4	10.9	15.8	11.2	—	10.5
Thymus (mg.)	—	715	500	659	392	517	378	485	301	350	—	215
Liver (gm.)	—	9.86	9.78	8.84	9.03	8.29	8.73	7.29	8.75	7.17	—	6.58
Kidneys (gm.)	—	1.72	1.83	1.58	1.62	1.47	1.66	1.36	1.64	1.36	—	1.28
Spleen (mg.)	—	626	586	544	635	581	602	510	598	449	—	534
Heart (mg.)	—	788	786	724	769	700	803	657	788	653	—	678
Number of rats in each group	—	6	11	32	15	19	13	12	12	28	—	14

putial glands were found to be atrophic (tables 1 and 2). The thymus is the only other organ which always undergoes an obvious change after ovariectomy, becoming hypertrophied and its involution retarded. This has been established by all authors, including Korenchevsky and his co-workers, and in the present experiments the same results were obtained.

The weights of most other organs have also been investigated by nearly all of the previously referred-to authors, and also by Bokelmann and Scheringer (9), Andersen and Kennedy (2), Winter and Emery (86), and Blumenfeld (7). Changes after ovariectomy in actual weight of the thyroid,

hypophysis, liver, kidneys, heart, brain, spleen, and alimentary canal cannot be considered of any significance because they are not always present, and if present, are only small, being in most cases a small increase, and less often a small decrease, in weight. Most authors have, however, mentioned that some decrease in the weight of most organs of spayed rats, as compared with those of normal controls, can be noticed when the weights are calculated per unit of body weight. In one paper Freudenberger and Hashimoto (28) give the relative weights of organs and examine the statistical significance of the changes obtained. They found a statistically significant decrease after ovariectomy in the brain, adrenals, thyroid, liver, and kidneys. Adrenals were found by some authors to be decreased even in actual weight (Hatai, 36; Andersen and Kennedy, 2; Freudenberger and Billiter, 25; Winter and Emery, 86; Freudenberger and Howard, 30; Blumenfeld, 7; Tang, 82). Various changes in the actual weight of adrenals were observed by Korenchevsky and his co-workers in previous and present experiments.

In the animal organism there is a normal ratio of the weight of each organ to the weight of the whole body, which probably represents the standard mass of the respective organ necessary for normal cooperation with, or control of, other organs and tissues. Obviously a decrease of this ratio would be a pathologic condition which sooner or later should produce pathologic changes in related organs and tissues.

Korenchevsky and his co-workers, comparing the weights of organs in normal and ovariectomised control animals, mentioned in previous papers that the relative weights of some organs are smaller in spayed rats. Since these weights have not previously been tabulated and summarised they are given in table 3. The data in this table cover only a small range of the life

TABLE 4. RELATIVE WEIGHTS OF ORGANS PER 200 GM. OF FAT-FREE BODY WEIGHT IN NORMAL AND OVARIECTOMISED RATS, AND IN OVARIECTOMISED RATS INJECTED WITH OESTRADIOL B.B. (ACTUAL WEIGHTS GIVEN IN TABLES 1 AND 2)

	Second Series of Experiments				First Series of Experiments		
		Ovariectomised rats			Ovariectomised rats		
	Normal Controls	Controls	Injected with oestradiol B.B.		Controls	Injected with oestradiol B.B.	
			medium dose	large dose		small dose	large dose
Fat-free body weight (gm.)	180	215	185	182	223	182	193
Uterus (mg.)	466	29	261	344	30	210	248
Vagina (mg.)	338	153	312	326	142	300	280
Preputial glands (mg.)	89	54	55	62	45	53	42
Adrenals (mg.)	67.8	51.2	90.8	76.9	52.0	60.4	82.9
Thyroid (mg.)	16.7	13.0	17.3	18.7	17.0	19.8	18.7
Hypophysis (mg.)	17.0	14.3	21.4	42.5	13.4	15.2	48.1
Thymus (mg.)	229	274	186	144	171	137	102
Liver (gm.)	7.71	6.32	8.66	8.79	6.83	6.56	8.68
Kidneys (gm.)	1.68	1.34	1.73	1.70	1.33	1.47	1.72
Spleen (mg.)	670	758	755	669	788	505	599
Heart (mg.)	871	714	879	778	726	860	811
Abdominal fat (gm.)	12.9	6.0	7.7	7.9	11.8	13.2	10.3

span. Since a different strain of rats was used in later experiments, the results could not be included in the same table. The present data have been tabulated separately in table 4, columns 1 and 2.

In table 3, weights of organs are calculated per 200 gm. of fat-free body weight, 200 gm. being chosen as a unit since it approximates the average weight of a rat. Body fat was excluded from body weight for two reasons: (1) When compared with a thin animal, the large fat deposition in the body of a fat animal will, when the organs are calculated per unit of body weight, simulate a fictitious decrease in the organs; and (2) the size and weight of an organ are determined to a lesser or greater extent by the amount of work which that organ has to perform independently of, or for the maintenance and functioning of, correlated organs and tissues; from this point of view the inert fat tissue cannot be compared with other active tissues such as glandular, muscular, and nervous tissue.

The fat-free body weight was obtained by subtracting the weight of total body fat from the body weight, assuming, according to Reed, Yamaguchi, Anderson and Mendel (70), that the dissected abdominal fat represents about 32 per cent of the total body fat. This fat-free method of calculation has been employed previously, in particular when establishing hypoplasia of organs in the process of aging in male rats (46).

Examination of data given in table 3 reveals the following: (1) Fat deposition increased with aging both in normal and ovariectomised animals without, however, development of "castration obesity." (2) During the short range of life span observed, the preputial glands and ovaries in normal female rats showed relative hypoplasia but not the uterus and vagina. Hypoplasia was seen in all the nonsex organs examined in ovariectomized rats, but was established only in thymus, liver, kidneys and hypophysis of normal rats. (3) Hypoplasia was more extensive in ovariectomised animals (except, of course, in the thymus, involution of which is always delayed by gonadectomy). For statistical analysis of differences between weights of organs in normal and ovariectomised rats the oldest group of rats was chosen (91–140 days old, table 3). For adrenals, thyroid, hypophysis, liver, kidneys, spleen and heart, P was <.001. However in the pres-

TABLE 5. EFFECTS OF AGING ON RELATIVE WEIGHTS OF ORGANS PER 200 GM. OF BODY WEIGHT IN NORMAL (N) AND IN OVARIECTOMISED (OV) FEMALE RATS (RECALCULATED AND SUMMARISED FROM DATA ON ACTUAL WEIGHTS GIVEN BY FREUDENBERGER ET AL. [25, 28, 30])

Average Age in Days	70		93		184	
Group of Rats	N	OV	N	OV	N	OV
Body weight (gm.)	156	185	171	250	213	249
Adrenals (mg.)	52.6	44.4	48.7	30.0	47.8	27.0
Thyroid (mg.)	20.3	18.7	21.2	16.0	19.6	15.8
Hypophysis (mg.)	12.2	12.3	10.3	8.3	10.9	9.4
Thymus (mg.)	718	1152	527	634	276	384
Liver (gm.)	9.62	9.15	7.92	6.08	7.63	6.22
Kidneys (gm.)	1.88	1.71	1.69	1.25	1.61	1.33
Spleen (mg.)	523	568	489	412	451	408
Heart (mg.)	941	930	836	646	800	718
Brain (gm.)	2.182	1.896	—	—	1.736	1.465
Number of rats in each group	25	25	24	24	25	25

ent experiments (table 4, columns 1 and 2), although differences were seen in the weights of all organs, these differences were statistically significant only in the case of the thyroid ($P < .001$), adrenals ($P < .01$), hypophysis ($P < .05$), liver ($P < .001$) and heart ($P < .001$). (4) Taking the progress of relative hypoplasia as a sign of aging, rats apparently age more rapidly after ovariectomy.

In order to confirm, for a longer period of the life span, that relative hypoplasia of organs develops progressively with aging in normal female rats, the actual weights of organs given by Donaldson (22) have been recalculated per 200 gm. of body weight (not fat-free, because Donaldson does not give weights of fat). In the case of older rats, the weights given by Donaldson for some organs were apparently not observed weights but calculated by formula. Therefore we have excluded the oldest groups (i.e., the heaviest rats). Since the age of the rats was not given, the following figures represent percentage decrease of certain organs from the age at which body weight is 25 gm. to the age when body weight is 301 gm.: adrenals 32, thyroid 42, liver 42, kidneys 37, spleen 16, heart 43, brain 87, alimentary tract 43, and pancreas 52. The relative weights of the sex organs given were heaviest at the age when body weight was 100 gm. From that age to the age when body weight was 301 gm., the decrease in relative weights of ovaries was 43, uterus 33, and vagina 50 per cent.

Thus, the relative weights from Donaldson's data show the same relative hypoplasia with aging of the organs of normal female rats which was described previously (46) in the normal male rat and which, in spite of the short period of observation, is already indicated in some organs of normal female rats in the experiments reported on in this paper. In these experiments a longer period of observation would almost certainly have given the same results as those in Donaldson's data. In a previous paper Korenchevsky (46, p. 19) found the same progressive hypoplasia of organs in women during the process of aging.

In order to confirm the observation that ovariectomised rats age more rapidly, the relative weights of organs were recalculated per 200 gm. of body weight from the actual weights given for normal and ovariectomised rats of different ages in three papers by Freudenberger, Billiter, Hashimoto, and Howard (25, 28, 30) and in a paper by Hatai (36). Hatai's data are more difficult to use since in his experiments the rats were spayed at different ages, and there was also considerable variation in the weight of organs among litters of about the same age. Therefore we have selected for recalculation only the data on those rats

TABLE 6. EFFECTS OF AGING ON RELATIVE WEIGHTS OF ORGANS PER 200 GM. OF BODY WEIGHT IN NORMAL (N) AND IN OVARIECTOMISED (OV) FEMALE RATS (RECALCULATED AND SUMMARISED FROM DATA ON ACTUAL WEIGHTS GIVEN BY HATAI [36])

Average age in days	132		156	
Group of rats	N	OV	N	OV
Body weight (gm.)	154	192	196	230
Adrenals (mg.)	65.0	47.9	48.9	36.9
Thyroid (mg.)	45.7	39.0	42.7	36.8
Hypophysis (mg.)	11.1	10.7	10.2	11.0
Thymus (mg.)	183	310	161	246
Brain (gm.)	2.137	1.779	1.773	1.564
Number of rats in each group	12	11	14	13

which have been spayed at the earliest age (19–30 days) and in which the groups consisted of not less than ten animals (Hatai's table 7). Unfortunately Hatai weighed only thyroid, adrenals, thymus, hypophysis and brain. These recalculated weights from experiments by Freudenberger, Billiter, Hashimoto, and Howard, and by Hatai have been summarized in tables 5 and 6 respectively, which tables are constructed like table 3.

Judging by the rate and degree of relative hypoplasia of organs, the data in tables 5 and 6 confirm that ovariectomy hastens the process of aging.

Effect of Thyroid Hormone.—The body weight, fat deposition and weight of various organs after administration of thyroid hormone have been investigated by Schäfer (74), Hoskins (42), Kojima (43), Herring (38), Cameron and Carmichael (11, 12), Cameron and Sedziak (14), Hashimoto (34), Cameron (15), Cowan (19), and Drill (23). The results obtained with both toxic and nontoxic doses in nearly all cases are in good agreement. Toxic effects produced by very large doses of thyroid hormone or by an insufficient supply of vitamins are of no interest for the purpose of the present experiments and will not be reviewed here.

Small doses of thyroid hormone either do not affect body weight and body growth or slightly accelerate it (74, 42, 38). Comparatively large but nontoxic doses depress the rate of growth.

The following organs examined become hypertrophied after administration of thyroid hormone: adrenals, liver, kidneys, heart, spleen, lymphatic glands, and pancreas. With weak doses hypertrophy is usually seen in relative weights of organs, but with larger doses it is seen both in relative and in actual weights. Body fat decreases, the larger the dose of thyroid hormone the greater being the loss of fat. The weight and size of the thyroid are often reported to be below normal. In the ovaries, hypertrophy of varying degree with increased formation of corpora lutea was observed by Herring (38), Hayashi (37), Weichert and Boyd (84) when small doses of thyroid hormone were administered, while large doses produced atrophy of the gonads.

Cameron and Carmichael (13) have made an important observation—namely, that whereas thyroid feeding decreased body weight in rats, after cessation of this treatment the body weight increased above normal, exceeding the values of control rats. At the same time hypertrophy of most organs nearly or completely disappeared during a period of from four to seven weeks after cessation of thyroid feeding.

Previous experiments on normal female rats (57) together with the present experiments on ovariectomised rats (tables 1 and 2) all confirm the aforementioned observations on the stimulating and hypertrophying properties of thyroid feeding, in nontoxic doses, on the adrenals, liver, kidneys, spleen, heart, and ovaries, with little or no effect on the body weight.

With small doses of thyroid, fat deposition was found to be unaffected (table 1), but with a larger dose fat deposition was decreased (53, and table 2 of this report). With small doses (table 1) the kidneys and heart were the first organs to show a statistically significant enlargement ($P < .01$). The larger dose (table 2) produced typical and statistically significant changes in all organs affected, both in actual ($P < .01$–$.001$) and in relative weights.

In addition to the size of the dose of thyroid hormone, the most important factor in producing the beneficial and nontoxic effects mentioned above is a sufficient supply of vitamins in the diet. The extensive literature on the relationship between vitamins and thyroid hormone, including an account of his own important experiments, has recently been summarised by Drill (23). His conclusions were also confirmed by Korenchevsky, Hall, and Clapham (53, 57). It must be emphasised that in the experiments reported on in the present paper the diet of the rats was rich in vitamins.

Effects of Androsterone.—Nelson and Merckel (68) and van der Woerd (87) have investigated the effect of androsterone on the weight of female sex organs. The former found no enlargement of the uterus but they and Woerd reported increased size of female preputial glands after administration of the hormone.

Korenchevsky and his co-workers have investigated, in detail, the action of androsterone on several organs of the female rat (33, 45, 51, 54, 55, 58, 73). A similar study has been made in the present paper. The uterus was found to be slightly enlarged with large doses (51, 54), but with weaker doses (tables 1 and 2) it was not changed at all. The increases produced in the vagina were significant ($P < .01$–$.001$). The female preputial glands have been found to be much hypertrophied ($P < .001$) and the liver, kidneys and heart increased in weight after administration of androsterone ($P < .02$–$.01$ in the present experiments). Changes in the spleen were variable, mostly an increase (as, for example, table 2, $P < .01$). On an average, fat deposition ($P < .05$) and final body weight were always slightly increased. On the contrary, the adrenals and thymus were smaller ($P < .02$, tables 1 and 2). In relative weights, after the administration of large doses of androsterone—7.5 mg. a week—(54), the same hypertrophic changes were found in the respective organs but to a lesser degree than with actual weights. With smaller doses of androsterone (present experiments) the increase in relative weights of organs becomes especially small (in most cases about 6–7 per cent above those of the control rats), or there may be no increase at all. This fact indicates that androsterone stimulates the growth of some organs, chiefly in proportion to the general increase in growth and weight of the animal. In some cases this proportion may be exceeded somewhat. Thus, on the evidence of changes in body weight, fat deposition and weight of organs, androsterone could be classified as a general growth-promoting compound except for its effect on the adrenals and thymus.

Effect of Oestrogens.—Body weight was found by all authors to be decreased after injection of oestrogens (Spencer, D'Amour and Gustavson, 79, 80; Zondek, 89; Freudenberger and Clausen, 26, 27; and Bogart, Lasley and Mayer, 8).

The ovaries, after oestrogen injection, were increased in weight in experiments on adult rats performed by Hohlweg (39), Wolfe (88), Selye, Collip and Thomson (75), and Ellison and Burgh (24), because of increased size and number of corpora lutea, but were found to be decreased or atrophic by Leonard, Meyer and Hisaw (62), Spencer, D'Amour, and Gustavson (79), Zondek (89), Freudenberger and Clausen (26), and Castillo and Sammartino (17). In experiments on immature rats, Selye, Collip, and Thomson (75) and Nelson and Hickman (67) observed large ovaries after a short period of treatment, but atrophic ovaries after prolonged injections of oestrone—that is, the effect depended on the number of doses.

While in normal female rats the uterus may be arrested in its development by oestrogens (79, 26), it is a well established fact that in ovariectomised rats the atrophic uterus and vagina always become hypertrophied.

The effects of oestrogens on the weight of nonsex organs, except adrenals, thyroid, hypophysis, and thymus, have been studied very little by previous workers. The adrenals were observed to be increased in weight according to some authors (61, 75, 1, 24, 3, 21, 17, 10, 31), but no change in weight was found by others (62, 26, 27, 4). Thyroids in oestrogen-injected rats were found to be enlarged (61, 69, 1), or lighter (5, 3, 17, 4, 26), or unchanged (24, 62).

The hypophysis of rats was observed to be enlarged, by all authors who injected sufficiently large doses of oestrogens. However, small doses did not produce any definite change (6, 61, 39, 88, 75, 66, 89, 90, 24, 17). The liver was larger in the experiments of Griffiths, Marks and Young (32).

The thymus was found to be decreased (16, 26, 60, 63, 18).

The brain, spleen and kidneys also weighed less in oestrone-injected rats according to Freudenberger and Clausen (26), but these authors found no change in the weight of the liver and heart. Ludden, Krueger and Wright (64) found heavier relative weight of kidneys in normal female rats injected with oestradiol benzoate, which increase they explain chiefly by retention of water in the renal tissue.

In the previously mentioned published and unpublished experiments of Korenchevsky and co-workers, pure oestrone, pure oestradiol, oestradiol dipropionate and oestradiol 3-benzoate-17-n-butyrate (oestradiol B.B.) were used in various doses. The detailed summary and analysis of the results obtained in these experiments, performed on 199 rats, will be made elsewhere. The weights of organs were recalculated per unit of fat-free body weight and will be referred to only briefly in order to confirm and substantiate the conclusions of this paper. There is complete agreement between previous results and those obtained in the present experiments.

Both previous and present experiments of Korenchevsky and his co-workers are in agreement with observations made by other workers, as to the depressing effect of oestrogens on body weight, the hypertrophying effect of oestrogens on the uterus and vagina, and, when sufficient doses are used, on the hypophysis (in the present experiments, $P < .01–.001$). Involution of the thymus was hastened (for example, tables 1 and 2, $P < .05–.01$), but the effect on actual weights of other organs and on fat deposition was found to be variable. In some cases the effect was indifferent or definitely depressing (liver $P < .05$), as, for example, when a small dose of oestradiol B.B. was injected (table 1, column 3). On the contrary, larger doses of this oestrogen increased the actual weights of adrenals ($P < .01–.001$) and liver ($P < .05–.01$) (see table 1, column 5, and table 2, columns 4 and 6). A similar significant increase in the actual weights of liver and kidneys was obtained previously (47) with oestradiol B.B. and oestradiol dipropionate.

Taking into consideration the depressing effect of oestrogens on body weight, the relative weights per unit of fat-free body weight would be likely to demonstrate more clearly the stimulating effects, if present, of oestrogens. These values are given in table 4. A comparison of columns 3 and 4 with column 2, and column 7 with column 5 of table 4 shows that a significant increase was obtained in the following non-sex organs: adrenals ($P < .01–.001$), thyroid ($P < .001$), liver ($P < .01–.001$), kidneys ($P < .01–.001$), and heart ($P < .02–.001$), and, of course, there was an obvious increase, with larger doses, in the hypophysis. Similar results were obtained by examination of relative fat-free weights in previous experiments (47, 54), in which slowly absorbed esters of oestradiol were used—dipropionate and especially benzoate butyrate. As in one of the present experiments, no definite results were obtained if too small a dose was injected. At the same time, with too large doses the general depressing effects obscured or even overcame the hypertrophying effect of oestrogens on some organs. Moreover the large doses produce such severe pathologic changes as huge enlargement of, and toxic changes in, the hypophysis, and toxic degenerative changes in the adrenals, liver, kidneys, uterus, etc.

Thus, to summarise, it must be concluded that oestrogens definitely have both stimulating and depressing properties. The latter may obscure the former. For production of a hypertrophying effect on organs, the slowly absorbed esters of oestradiol, especially benzoate butyrate, in suitable doses are most efficacious. The weight of organs per unit of fat-free body weight demonstrates more clearly these hypertrophying effects, although in some cases they are clearly seen in actual weights as well.

Correlative Effects of the Hormones

Correlation of Thyroid Hormone and Oestradiol.—No data were found in the literature on the combined effect of these two hormones on the weight of organs in the rat. There are however some other data which suggest apparently antagonistic effects. Thus, in order to produce oestrus in rats which are in a state of experimental hyperthyroidism, a much larger dose of oestrone is necessary (van Horn, 41; Meyer and Wertz, 65). In rats treated with oestrogens, administration of thyroid hormone produces a less pronounced rise of gaseous metabolism than in nontreated animals (Danforth, Green, and Ivy, 20; Sherwood, 76, 77).

In the experiments discussed in the present paper, the results obtained suggest, on the contrary, cooperative activity. After the simultaneous administration of oestradiol B.B. and a large dose of thyroid hormone (table 2), the uterus and the vagina ($P < .05$) were slightly larger than with administration of oestrogen alone. A small dose of thyroid (table 1) did not produce the same effect. The cooperative effect in enlarging the adrenals was especially marked (tables 1 and 2, $P < .01$–$.001$), both in actual and in relative weights. In particular it must be emphasised that small doses of thyroid and oestradiol B.B., when given separately (columns 2 and 3, table 1), had no effect at all, while the combined action of the two (column 4) resulted in large adrenals ($P < .001$). Larger doses of cestradiol and thyroid, however, when administered separately produced a considerable effect on the weight of the adrenals, and together had a much greater cooperative effect than with small doses. A similar correlation (tables 1 and 2) is suggested with some doses in the case of the liver and kidneys. In these organs the relative weight, or both actual and relative weights, was greater after the simultaneous administration of the two hormones than when either was given separately. It must, however, be emphasised that this difference was either statistically insignificant or just significant ($P < .05$) when comparison was made with weights of organs in rats treated with thyroid hormone alone (column 2, table 1; column 3, table 2).

The heart, after combined treatment with the two hormones, was usually no larger in weight than after administration of thyroid alone. The weight of the spleen, decreased by oestrogens, returned toward normal or even exceeded normal weight ($P < .02$–$.01$), both in actual and in relative weights, when the two hormones were given together.

A lack of any correlation of oestrogen and thyroid hormones was recorded in the case of weights of other organs examined and in fat deposition. In the case of oestrogenic involution of the thymus and oestrogenic hypertrophy of the hypophysis (tables 1 and 2), these effects were influenced in no way, simultaneous administration of oestrogen and thyroid hormone producing the same effect as that obtained with oestrogens alone.

Correlative Effects of Androsterone and Thyroid Hormone.—No reference to work on this subject has been found in the literature.

After combined treatment with the above hormones, the weights of sex organs and thymus in the experiment presented in this paper were found to be similar to those of rats treated with androsterone alone. The weights of nonsex organs were similar to those in animals treated only with thyroid hormone, when a large dose of the latter was administered (table 2). The slight increase in weight of the liver, kidneys, and heart after simultaneous injections of androsterone and a small dose of thyroid hormone (table 1) may suggest an additive effect. In this case, the powerful effect of the large dose of thyroid hormone did not change the weaker correlative effect of androsterone.

There is, however, one important effect of an antagonistic nature which must be emphasised. Large doses of thyroid hormone are able to neutralise the hypoplastic

effect of androgens on the adrenals (table 2, columns 8 and 9).

Correlative Effects of Androsterone, Oestradiol and Thyroid Hormones.—No data relating to the simultaneous administration of these three hormones have been found in the literature, nor, apart from publications by Korenchevsky and his co-workers (51, 54, 55), on the effects of androsterone and oestrogens on female rats. Korenchevsky and co-workers found that simultaneous administrations of androsterone and oestrogens, as compared with treatment by androsterone or oestrogens alone, produced a larger uterus and vagina and a smaller thymus, neutralised the depressing effects of oestrogens on actual weights of liver, spleen, heart, fat deposition and body weight, decreased the oestrogenic hypertrophying effect on the hypophysis, and caused hypoplastic adrenals to return toward normal or even to exceed the normal weights. When calculated per unit of fat-free body weight some of these changes were the same as when calculated in actual weights, as in the case of the sex organs, adrenals, hypophysis and thymus. In the liver, kidneys, and heart (as mentioned in the previous section on effects of oestrogens) these fat-free weights show an increase after oestrogen administration, and this increase remains of about the same degree after simultaneous administration of oestrogens and androsterone.

In the experiments here reported on, simultaneous administration of the three hormones produced changes in weights of organs similar to those obtained after treatment with two hormones only (oestradiol and larger dose of thyroid hormone —compare columns 5 and 10, table 2) in the case of the liver, kidneys, spleen and heart. A slight intensification in these changes is seen when compared with the effect produced by oestradiol and a small dose of thyroid hormone (compare columns 4 and 9, table 1). This probably indicates the additive effect of androsterone, which is not apparent with the larger dose of thyroid hormone because the powerful effect of the thyroid hormone obscures the much weaker effect of androsterone. This additive effect of androsterone was also indicated in a slight increase of weight in the uterus and vagina (vagina–$P < .05$), larger fat deposition, and increase in body-weight.

Since changes in weight per unit of fat-free body weight as compared with changes in actual weights are less pronounced or absent, the additive effect of androsterone, when seen in actual weights, can be explained by a better growth of the organs in proportion to the increased growth of the whole body. This is in good agreement with the effects of androsterone when this hormone was injected alone, as demonstrated in a previous section of this paper.

Summary

1. Experiments were performed on 11 normal and 108 ovariectomised rats. A re-examination and recalculation were made of the results of some previous experiments, of a similar nature, on 54 normal and 325 ovariectomised rats.

2. The condition produced in the young or adult female organism by ovariectomy might be considered as an artificial, premature and extreme climacteric of purely ovarian origin.

3. For the normal and ovariectomised rat, the data of our experiments and those recalculated from actual weights of organs given by Donaldson and by Freudenberger and co-workers all demonstrate the same progressive relative hypoplasia of organs in the process of aging as that previously described for the normal male rat, and for men and women. Thus the relative hypoplasia of organs may be considered to be one of the essential features or indicators of aging.

4. In ovariectomised rats as compared with normal animals, body weight is increased and fat deposition variable ("fat" or "thin" castrates); involution of the thymus is delayed, and the weight of most other organs examined is found to be de-

creased, when calculated per unit of fat-free body weight.

5. Ovariectomised rats apparently age more rapidly than normal rats, since in the former, the hypoplasia of organs that comes with aging is greater than in normal animals.

6. The hypertrophying and depressing properties of oestradiol esters, androsterone and thyroid hormone, and the differences in their action on ovariectomised rats, as shown by changes in body weight, fat deposition and weight of organs, have been analysed.

7. Correlative effects of oestradiol B.B. and thyroid hormone are demonstrated in the increased enlargement of adrenals and, with some doses, of vagina, liver and kidneys.

8. In general, the simultaneous administration of the three hormones used is characterised by the hypertrophying effects on organs which are produced by the two more powerful compounds, oestrogenic and thyroid hormones; the enhancing effects of androsterone on weights of organs are noticeable only with small doses of oestrogenic and thyroid hormones. In particular, oestrogenic and thyroid hormones, when administered separately or simultaneously, neutralise the depressing effect of androsterone on the adrenals.

9. By selecting a suitable dose, combining with other hormone or hormones, and using slowly absorbed compounds of oestradiol, it may be possible to use predominantly the hypertrophying properties of androsterone, oestradiol and thyroid hormone.

10. In this way there appears to be a possibility of overcoming, for a length of time not yet investigated, the hypoplasia of several organs in the artificial premature climacteric of ovarian origin, produced by ovariectomy in the rat.

11. When using hypertrophying hormones (in order, for example, to investigate their effects on the hypoplasia of aging), it is important to avoid the pathologic changes which may be produced by these hormones if unsuitable doses and combinations of hormones are employed—for example, changes in hypophysis and metaplasia of epithelium produced by oestrogens, hypoplasia of adrenals produced by androgens, and loss of fat and body weight produced by thyroid hormone.

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The Effects of Androsterone, Oestradiol, and Thyroid Hormone on the Artificial Premature "Climacteric" of Pure Gonadal Origin Produced by Ovariectomy in Rats

II. Effects on Histologic Structure of Liver and Kidneys

VERA E. JONES AND V. KORENCHEVSKY

IN EXPERIMENTS MADE ON 108 OVARIECTOMISED AND 11 NORMAL RATS, IT WAS FOUND THAT THE ADMINISTRATION OF THREE HORMONES—THYROID, ANDROSTERONE, AND ESTRADIOL—WAS EFFECTIVE IN DELAYING OR REVERSING THE DECREASE IN RELATIVE WEIGHT OF THE LIVER AND KIDNEY WHICH OCCURS AS A RESULT OF THE ARTIFICIAL CLIMACTERIC PRODUCED BY OVARIECTOMY AND/OR AS A RESULT OF NATURAL AGING. THYROID WAS FOUND TO STIMULATE CELL REPRODUCTION, WHICH HAD BEEN DECREASED BY OVARIECTOMY, WHILE ANDROSTERONE AND ESTRADIOL INCREASED THE SIZE OF THE CELLS WITHOUT APPARENT EFFECT ON THE NUMBER OF MITOSES. IN THE ARTIFICIAL CLIMACTERIC IN THE RAT, THE THREE HORMONES APPEARED TO BE EFFECTIVE IN PREVENTING HYPOPLASIA OF THE LIVER AND KIDNEY CELLS AND IN PRODUCING AN ENLARGEMENT OF THE LIVER AND KIDNEYS ABOVE THE LEVEL FOUND IN NORMAL ANIMALS.

IN OUR previous paper, pages 319–335 of this issue (10), the effects of androsterone, oestradiol, and thyroid on the weight of organs were investigated. In the present paper results of histologic examination of changes produced by the hormones in the liver and kidneys are given. This histologic examination was carried out on the same 119 rats described and summarised in tables 1 and 2 of the previous paper. As in the previous paper a review of the literature referring to each of the hormones used will precede the description of the results obtained.

In the histologic examination especial attention was paid to measurement of cells and nuclei and to estimation of the number of mitoses, the reason being that the hypertrophying or hyperplastic effects of the hormones are important with regard to the age-induced hypoplasia and atrophy of the cells and particularly of the nuclei, since the nucleus is the most vital part of the cell.

MATERIAL AND METHODS

The arrangement of the experiments into groups, the doses of hormones administered, and some other details are given in tables 1 to 3 and also in the previous paper, in the section on technique.

The organs were fixed in Bouin's fixative and embedded in paraffin, the sections cut at 5μ thickness and stained with Ehrlich's haematoxylin and eosin. Frozen sections were also cut and stained with sudan black for fatty substances.

The usual histologic examination and count of mitoses was made on all of the 119 rats, but detailed measurement of cells and nuclei was made in only 116 rats in the case of the liver, and in only 60 rats in the case of the kidneys. Measurements of the liver cells and renal tubules were made by outlining them on special paper, with the aid of a camera lucida, at a mag-

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Dr. V. Korenchevsky, a Russian by birth, was formerly professor of experimental pathology at the Imperial Medical Academy in Petrograd. He received his M.D. degree from Moscow University. In 1920 he emigrated to England, becoming a naturalized British citizen. He was senior research worker at the Lister Institute of Preventive Medicine in London. He was an initiator of and active in the foundation, in 1939, of the Club for Research on Ageing, with branches in Europe, the United States, and Argentina. Dr. Korenchevsky is now Hon. Secretary of the British branch. In 1945 he was appointed head of the Gerontological Research Unit at Oxford, establishment of which was made possible by a grant from Lord Nuffield. Hospitality has been extended to the Unit by Prof. A. C. Hardy and Prof. E. G. T. Liddell of the department of zoology and the department of physiology at Oxford University. The subjects of research in which Dr. Korenchevsky is most interested include endocrinology, the study of vitamins, and gerontology.

Ciba, Ltd., in particular Dr. K. Miescher, supplied the hormones used in the experiments here reported on, and Parke, Davis, and Co. supplied the desiccated thyroid.

nification of 720 (liver) and 390 (kidneys). These paper replicas were then cut out and weighed. A sample of standard area from each sheet of paper used was also cut out and weighed. When computing the averages of paper replicas, all weights were corrected to a standard weight of paper. The middle part of the same small lobe was cut out and embedded for sectioning. Cells for outlining were chosen from the middle zone between the central vein and the periphery of the lobule, all cells from the fields taken being drawn whenever possible. Only transverse sections of renal proximal tubules were outlined, the paper replicas of the tubules and lumens being cut out and weighed separately. Not less than 150 liver cells and 60 renal tubules were outlined for each rat.

As a standard size of "large" liver cell or nucleus, that size was taken which was found to be approximately in the minority in normal rats. Thus "large" liver cells were taken to be those which measured $21 \times 21\mu$ and over, if roughly spherical in shape, or $28 \times 14\mu$ and over, if oblong. "Large" nuclei were those of diameter greater than 6.2μ in the renal cells and equal to or greater than 8.3μ in the liver cells. The renal nuclei were outlined at a magnification of 970 and the hepatic nuclei, at a magnification of 720. The outlined cells and nuclei were measured in millimeters and the measurements converted into microns when necessary.

Mitoses were counted, depending on the size of the liver or kidneys, in the whole of one to three transverse sections. The areas examined were then measured by means of a planimeter and the percentage of mitoses calculated for a standard area.

For statistical significance of the changes obtained, the values of experimental or normal groups were compared with the group of control ovariectomised rats (unless otherwise stated).

Effects of Ovariectomy and of the Hormones Administered Separately

Effect of Ovariectomy.—The structure of the liver cells of normal rats differs from that of ovariectomised animals (table 2, lines 1 and 2) only by an increase in the number of large nuclei ($P < .02$) and by a greater number of mitoses ($P < .05$).

In the kidneys (table 3, lines 1 and 2) larger renal tubules ($P < .01$) and an increased number of mitoses ($P < .001$) were recorded in normal rats. These findings are in good agreement with the decrease in relative weights of these organs after ovariectomy (10).

Effect of Thyroid Hormone.—The lit-

TABLE 1. EFFECT OF ANDROGENIC, OESTROGENIC AND THYROID HORMONES, ADMINISTERED SEPARATELY OR SIMULTANEOUSLY ON LIVER CELLS

Weekly doses of hormones: Desiccated thyroid 105 mg. = "small dose"; Oestradiol B.B. 0.015 mg. injected for first 3 weeks only = "small dose"; Oestradiol B.B. 0.09 mg. injected every week = "large dose"; Androsterone 4.5 mg.

Group of rats and dose of hormone	Weight of liver (gm.)	Weight of paper replica of average cell (mg.)	Percentage of large cells	Percentage of large nuclei	No. of mitoses in standard measured area	No. of rats in group
1. Ovariectomised controls	7.61	6.9	12.5	18.9	0	8
2. Thyroid hormone small dose	7.94	7.3	19.6	47.5	0.7	10
3. Oestradiol B.B. small dose	5.97	6.5	6.3	33.1	0	5
4. Oestradiol B.B. small dose + thyroid small dose	7.27	7.0	16.2	56.2	6.4	5
5. Oestradiol B.B. large dose	8.38	7.7	25.3	47.1	0.2	4
6. Oestradiol B.B. large dose + thyroid small dose	9.00	7.6	27.6	65.1	5.6	5
7. Androsterone	8.51	8.3	30.7	38.2	0	6
8. Androsterone + thyroid small dose	9.44	7.9	31.3	52.3	0.2	6
9. Androsterone + thyroid and Oestradiol B.B. small doses	8.21	7.6	23.2	58.1	3.5	7

TABLE 2. EFFECT OF ANDROGENIC, OESTROGENIC AND THYROID HORMONES, ADMINISTERED SEPARATELY OR SIMULTANEOUSLY ON LIVER CELLS

Weekly doses of hormones: Desiccated thyroid 250 mg. + Thyroxine 0.8 mg. = "thyroid hormone large dose"; Oestradiol B.B. 0.015 mg. injected for first 3 weeks and last 2 weeks = "medium dose"; Oestradiol B.B. 0.09 mg. injected every week = "large dose"; Androsterone 4.5 mg.

Groups of rats and dose of hormone	Weight of liver (gm.)	Weight of paper replica of average cell (mg.)	Percentage of large cells	Percentage of large nuclei	No. of mitosis in standard measured area	No. of rats in group
1. Normal controls	7.17	6.7	19.4	52.5	3.7	8
2. Ovariectomised controls	6.79	6.4	22.8	35.9	0.5	7
3. Thyroid hormone large dose	9.17	7.2	25.5	59.9	11.0	7
4. Oestradiol B.B. medium dose	8.01	7.5	31.5	46.1	4.7	6
5. Oestradiol B.B. medium dose + thyroid hormone large dose	11.55	8.1	42.8	72.0	8.3	6
6. Oestradiol B.B. large dose	8.00	7.2	27.6	49.2	1.2	4
7. Oestradiol B.B. large dose + thyroid hormone large dose	9.68	7.5	34.0	62.2	7.1	4
8. Androsterone	8.78	7.4	28.8	45.1	0.7	6
9. Androsterone + thyroid hormone large dose	9.99	6.6	23.2	66.7	7.1	6
10. Androsterone + thyroid hormone large dose + Oestradiol B.B. medium dose	10.57	6.9	24.4	63.8	27.5	6

erature on histologic changes in the liver and kidneys, produced by thyroid hormone, has been reviewed and summarised by Korenchevsky and Hall (8).

When toxic doses of thyroid hormone have been used, certain changes in the liver have been recorded, the results of different workers being in good agreement with each other. These changes include depletion of glycogen, congestion, perivascular oedema, degeneration, atrophy and necrosis of the cells, cellular infiltration between the lobules, and cirrhotic changes. With less toxic doses or doses given for only a short period, the changes consisted of enlargement of some of the cells, increased number of mitoses, cloudy swelling, and disappearance of basophilic granulation from the cells. The outlines of trabeculae and cells became indefinite.

In the kidneys, after administration of toxic doses, various degenerative changes resulting in some cases in necrosis have also been described.

With nontoxic doses, Cameron and Carmichael (1) found no changes in the structure of liver and kidneys of the one rat examined. Kastert (6) records disappearance of basophilic granulation in liver cells and variation in the number of fat droplets. Korenchevsky and Hall (8) found that in normal female rats, nontoxic doses of thyroid hormone produced considerable hyperplasia of liver cells but hypertrophy of kidney cells, thus explaining the mechanism of the general enlargement obtained in both liver and kidneys. The nuclei, both in liver and kidneys, were also hypertrophied, but the number of mitoses was significantly greater only in the liver. The cytoplasm of the liver cells underwent more or less pronounced structural changes, consisting of a decrease of fatty granulation, dissolution of basophilic granulation, and appearance of slight haemotoxylinophilic properties of the cytoplasm. These changes, together with the increased number of large nuclei and mitoses, give a special picture in the liver cells, characteristic of the effect of comparatively large but nontoxic doses of thyroid hormone.

In the experiments here reported on, a

TABLE 3. EFFECT OF ANDROGENIC, OESTROGENIC AND THYROID HORMONES ADMINISTERED SEPARATELY OR SIMULTANEOUSLY, ON PROXIMAL KIDNEY TUBULES

The same groups and doses as in table 2

Groups of rats and dose of hormone	Weight of kidneys (gm.)	Weight of paper replica of		Percentage of large nuclei	No. of mitoses in standard measured area
		average tubule (mg.)	average lumen (mg.)		
1. Normal controls	1.57	6.92	1.01	6.7	3.0
2. Ovariectomised controls	1.44	6.11	1.16	7.8	0
3. Thyroid hormone large dose	2.12	8.41	1.71	17.3	0.5
4. Oestradiol B.B. medium dose	1.60	6.87	1.10	13.3	0.2
5. Oestradiol B.B. medium dose + thyroid hormone large dose	2.54	8.57	1.71	29.7	0.6
6. Oestradiol B.B. large dose	1.55	7.27	1.39	24.0	0.2
7. Oestradiol B.B. large dose + thyroid hormone large dose	2.17	8.95	1.58	38.2	1.0
8. Androsterone	1.65	6.96	1.54	13.3	0.3
9. Androsterone + thyroid hormone large dose	2.18	8.78	1.55	25.1	0.4
10. Androsterone + thyroid hormone large dose + oestradiol B.B. medium dose	2.60	8.37	1.76	22.6	2.5

small dose of thyroid hormone (table 1, line 2) produced only one definite change in the liver cells—an increased number of large nuclei ($P < .001$). A slight increase in the size of the cells, in the percentage of large cells and in the number of mitoses was not statistically significant. This is in agreement with the lack of significant increase in weight of the liver.

With a large dose of thyroid hormone (table 2, line 3), not only was an increased number of nuclei recorded ($P < .01$) but also a greater number of mitoses ($P < .05$). The slight increase in size of cells and number of large cells was not statistically significant. Therefore the considerable increase in weight of the liver produced by the large dose must be explained chiefly by hyperplasia and not by hypertrophy of the liver cells.

In the kidneys (table 3, line 3), on the contrary, hypertrophy of renal tubules ($P < .001$) and not hyperplasia is responsible for the large kidneys of rats given thyroid hormone, the change in number of mitoses being insignificant. Not only was the cytoplasm of the tubule cells found to be hypertrophied, but the lumens of the tubules were enlarged ($P < .01$) and the number of large nuclei increased ($P < .05$). No other histologic changes were found in the kidneys.

Thus, in ovariectomised rats, after administration of thyroid hormone the same changes in liver and kidneys were obtained as those previously produced in normal rats (8).

It is worthy of mention that MacKay and Sherill (14) found a direct correlation between thyroid function and function of the kidneys. Hence, for example, they could increase renal function in hypothyroid patients by administration of thyroid hormone. Heinbecker, Rolf, and White (5) came to similar conclusions in experiments on dogs.

Effects of Androsterone.—At the present time the nephrotrophic properties of testosterone and its esters have been firmly established by different workers. The histologic examination of nephrotrophic and hepatotrophic effects of androsterone in female rats was made in previous experiments (9, 11). These results are in complete agreement with the experiments described in this paper. Hypertrophy of liver cells after androsterone administration was quite definite ($P < .01$–$.001$; table 1, line 7, table 2, line 8) and the number of large nuclei was also increased ($P < .01$, table 1), but there was no change in the number of mitoses. Likewise, the kidney tubules were enlarged (table 3, line 8, $P < .05$) and their lumens increased in size ($P < .02$).

Thus the large livers and kidneys in rats treated with androsterone may be explained chiefly by hypertrophy of the cells.

Effect of Oestrogens.—Griffiths, Marks, and Young (3) found considerably enlarged livers in rats, accompanied by an increase in liver glycogen, after administration of oestrone, oestriol or oestradiol. Guilder and Phillips (4) and Teague (18) also recorded a higher level of glycogen in livers after oestradiol injections. Teague describes glycogen deposition as taking place in the cells at the periphery of the small hepatic lobules. In sections which were not specially fixed and stained to show glycogen, the cells in these areas contained several vacuoles from which the glycogen had been washed out. Morrell and Hart (15) found, with small doses of oestrone, some blurring of cell outlines and thinning of cytoplasm in the hepatic cells of female rats. With large doses they observed degenerative changes in the liver. That the degenerative changes in the liver appear only after administration of large doses of oestrogens was confirmed also by other workers (2, 13, 17, 18). Pfeiffer, Emmel, and Gardner (16) recorded a slight increase in the relative weight of kidneys of mice treated with oestradiol benzoate or dipropionate, but they did not mention any histologic changes in these organs, nor did they find any changes in the water content. Ludden, Krueger, and Wright (12), on the contrary, explain an increase in relative weight of the kidneys in female rats treated

with oestradiol benzoate, by retention of fluid in the renal tissue, since chemical analysis indicated an increased water content in the kidneys, while histologically peritubular oedema was found in some places in the cortex. Korenchevsky, Hall, Burbank, and Cohen (9) found a decrease in the size of liver cells with some doses of cestradiol esters, and an increase with other, less toxic doses. At the same time, a decrease or depletion of fatty granulation in the liver cells was recorded with all doses used. Similar results were obtained in the experiments reported on in the present paper. Thus, with the smallest dose used (table 1, line 3) an insignificant decrease in size of the cell and number of large cells was found, but with all other doses an increase (from 11.6 to 17.2 per cent as compared with the spayed controls) in the size of the cells was recorded. This increase in cell size was significant, however, in only one case ($P < .02$, table 2, line 4). The number of large nuclei was increased in all cases, but this increase was significant in only one case ($P < .01$, table 1, line 5).

Therefore, hypertrophy of the cells is probably the chief reason for the large liver in rats treated with oestrogens, the increased glycogen deposition being also responsible to some extent perhaps.

Korenchevsky and Ross (11) were unable to find any change in the size of the tubules after administration of oestrogens, but they recorded some cystic degeneration, more or less pronounced, in the tubules of the innermost cortical portion of the kidneys.

However, in the experiments reported on in this paper, in both groups examined (table 3, lines 4 and 6) the convoluted tubules were found to be enlarged ($P < .05$–$.01$) without significant increase in the size of the lumens. The number of large nuclei and the number of mitoses were increased but not significantly so. No evidence of oedema was found. At the same time, cystic degeneration was observed in only 3 rats out of 19 and was slight in degree.

In summarising, the counteracting properties of oestrogens, depression and stimulation, must be emphasised. The final effect produced will therefore depend upon the predominance of one or other of these properties.

Hypertrophy of the tubule cells easily explains large kidneys after administration of oestrogens. Probably the slight hypertrophy of liver cells and perhaps the increased glycogen deposition are chiefly responsible for large livers after oestrogen administration.

Since the final effect of similar doses and compounds of oestrogens is not always the same in degree or in character, the individual resistance of some rats or litters of rats to the depressing action of oestrogens may also play a part.

Correlative Effects of the Hormones

Correlation of Thyroid Hormone and Oestradiol B.B.—This correlation was definitely demonstrated both in liver and kidneys.

In the liver the depressing effect of a small oestrogenic dose (table 1, line 3) on the size of the cells was overcome by simultaneous thyroid administration (line 4, $P < .01$), but the increase obtained was not greater than the effect of thyroid hormone administered alone (line 2). In other cases some additional effects could be seen. Thus with small thyroid hormone and large oestradiol doses (table 1, line 6) these values were significantly increased (large cells $P < .01$, large nuclei $P < .001$ and mitoses $P < .01$), while separately these two hormones produced a significant increase in number of large nuclei only. In the case of simultaneous administration of large thyroid hormone and medium oestradiol doses (table 2, line 5), or of large thyroid and large oestradiol doses (table 2, line 7), significant increases were seen in all four values examined (size of cells $P < .01$–$.001$, large cells $P < .05$–$.001$, large nuclei $P < .05$–$.001$, mitoses $P < .02$–$.01$). As demonstrated in the section on thyroid hormone, a large dose of this hormone alone increased

significantly only two values, while small doses of oestradiol produced no significant increase in any of the values examined (table 2, line 6) and large doses of oestradiol produced an increase only in the size of the cells (table 2, line 4).

In the kidneys (table 3), after simultaneous administration of the two hormones, changes in the size of tubules and lumens ($P < .05$) were about the same as those seen after administration of thyroid hormone alone. An additive effect, however, was seen in the increased number of large nuclei ($P < .02$–$.01$) and number of mitoses ($P < .001$), which were not significantly increased when either hormone was administered alone.

Thus in both organs after administration of oestrogenic and thyroid hormones combined, the enlargement was produced by both hypertrophy and hyperplasia of the cells.

Correlation of Thyroid Hormone and Androsterone.—In the case of liver cells, correlation of thyroid and androsterone produced different effects according to whether small doses (table 1, line 8) or large doses (table 2, line 9) were used. With small doses there was hypertrophy of the cells ($P < .01$) and an increased number of large cells ($P < .01$), the changes indicating the effect of androsterone. With large doses, hyperplasia (increased number of mitoses, $P < .02$) was responsible for the enlarged livers, the effect of the large thyroid hormone dose dominating that of androsterone. With both small and large doses the number of large nuclei was also increased ($P < .001$) to a slightly higher level than with thyroid hormone alone. The effect of these two hormones on the kidneys (table 3, line 9) was characterised by greatly increased size of the tubules ($P < .001$) similar to that obtained with the large thyroid dose alone. The lumens of the tubules were also enlarged ($P < .05$) and the number of large nuclei increased ($P < .02$). Since the number of mitoses was not increased significantly, hypertrophy of the tubules appears to be the reason for the enlarged kidneys.

Thus after combined administration of the two hormones, the hypertrophying effect of androsterone can be seen only with the small thyroid hormone dose, since the powerful effect of the large thyroid hormone dose dominates the weaker action of androsterone.

Correlation of Thyroid Hormone, Oestradiol B.B. and Androsterone.—Ludden, Krueger, and Wright (12) in experiments on female rats obtained larger kidneys after simultaneous administration of testosterone propionate and oestradiol benzoate than after treatment with either hormone alone. On gross histologic examination diffuse enlargement of renal elements and relative hyperaemia were seen. The effects of simultaneous administration of androsterone and oestrogens on the histologic structure of liver and kidneys of female rats have been studied previously by Korenchevsky and co-workers (9, 11). Unfortunately these studies included no count of mitoses. The hypertrophying effect of androsterone on the size of kidney tubules was shown, but no effect was seen on the size of liver cells. It was observed that androsterone also neutralised the degenerative changes in the kidneys produced by oestrogens, but this neutralising effect was recorded in only some of the injected rats.

In the experiments here reported on, after administration of all three hormones together, changes were seen in the liver cells similar to those produced by the combined action of androsterone and thyroid hormone previously described. With the small thyroid hormone dose the effect of androsterone was seen, since large livers were produced chiefly because of hypertrophy of the cells ($P < .02$, table 1, line 9) and an increased number of large cells ($P < .05$), the increase in number of mitoses being insignificant. With the larger dose of thyroid hormone (table 2, line 10), however, hyperplasia (increased number of mitoses, $P < .01$) was chiefly responsible

for the increase in size of the liver, the effect of the thyroid hormone predominating. In both cases the increase in the number of large nuclei ($P < .001$) was approximately the same as that seen with androsterone and thyroid hormone alone.

Both hypertrophy of the tubules ($P < .001$) and hyperplasia of the cells ($P < .001$) were responsible for the enlarged kidneys produced after administration of the three hormones together. The lumens of the tubules were greater ($P < .01$) and the number of large nuclei increased ($P < .001$). Except for the increased number of mitoses the other values did not exceed those obtained with a combination of thyroid hormone with either of the other two hormones (table 3, lines 5 and 9).

Basophilic and fatty granulation are the only features in the structure of the liver cells in which some variation has been observed.

Basophilic granulation in liver cells (7) is probably connected with storage and metabolism of proteins in this organ. As compared with control ovariectomised rats both basophilic granulation and fatty granulation appeared, in the experiments here reported on, to be better developed in the liver cells of rats treated with androsterone. This suggests that androsterone may have a storage effect. Both types of granulation were decreased, in varying degree, in the livers of rats to which large doses of thyroid hormone, alone or in combination with oestradiol, had been given. A pronounced decrease in fatty granulation but not in basophilic granulation was a typical effect of oestradiol. In all combinations of other hormones with androsterone, fatty granulation was also increased.

Summary

1. Histologic investigation of liver and kidneys in 119 female rats was made in order to study in detail the effects of thyroid hormone, androsterone and oestradiol B.B., alone or in various combinations, on the artificial premature climacteric of pure ovarian origin produced by ovariectomy.

2. In the liver, ovariectomy decreased the number of large nuclei and mitoses, producing relative hypoplasia. In the kidneys, smaller renal tubules and decrease in the number of mitoses probably explained the relative decrease in size.

3. The depressing and stimulating properties of oestradiol B.B., the hypertrophying properties of androsterone, and the hypertrophying and hyperplastic properties of thyroid hormone on the cells of liver and kidneys have been described and their effects compared.

4. Although some cooperative effects were observed, especially between oestradiol and thyroid hormone, it was found that in general, in the combinations of hormones used, the effects of the larger dose of thyroid hormone predominated over the effects of oestradiol and androsterone. With a small dose of thyroid hormone, some correlative effect of androsterone was indicated.

5. Oestrogenic hormones deplete, more or less completely, fatty granulation in the liver cells, while androsterone alone or in combination with other hormones apparently increases both fatty and, to a lesser extent, basophilic, granulation. Thyroid hormone in large doses decreases basophilic granulation and has a variable effect on fatty granulation.

6. In the artificial climacteric in the rat, the hormones used appear to be effective not only in preventing hypoplasia of liver and kidney cells, but also in producing an enlargement which is over and above the level observed in normal animals.

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Histochemical Changes Associated with Aging

IV. Liver, Brain, and Kidney in the Rat

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THE PRESENT REPORT BY DR. LOWRY, DR. HASTINGS, DR. McCAY AND MISS BROWN FOLLOWS OTHERS MADE ON THE HISTOCHEMICAL CHANGES ASSOCIATED WITH AGING IN THE MUSCLE OF THE RAT. IN THE PRESENT INVESTIGATION, CHEMICAL ANALYSES OF THE LIVER, BRAIN, AND KIDNEY WERE PERFORMED FOR SODIUM, CALCIUM, MAGNESIUM, ETC., AND CALCULATIONS OF TOTAL INTRACELLULAR AND EXTRACELLULAR MATERIAL WERE MADE. LITTLE OR NO CHANGE WAS OBSERVED IN THE COMPOSITION OF THE LIVER AND BRAIN WITH SENESCENCE. HOWEVER, SENESCENCE PRODUCED IN THE KIDNEY A CONSPICUOUS DECREASE IN THE RELATIVE MASS OF THE CELLS.

IN AN earlier report (1) data were presented which led to the conclusion that in rat skeletal muscle, aging is associated with a marked decrease in the relative mass of fibers with concomitant increase in extracellular fluid. In spite of these changes there appeared to be little or no change during senescence in the concentration of water, total phosphorus, and potassium in the muscle fibers.

The data on which these simple conclusions were based would have been exceedingly confusing without the benefit of the "deductive histochemical method" by which gross tissue data may be used to provide an estimate of the mass and composition of the extracellular and intracellular phases (Peters (2), Fenn, Cobb, and Marsh (3), Eggleton, Eggleton, and Hamilton (4), Hastings and Eichelberger (5), Yannet and Darrow (6), Muntwyler, Mellors, Mautz, and Mangun (7)). The tissue cells have a chemical composition differing so radically from the surrounding fluid that when analyzed together, as they must be in whole tissue analyses, changes in the proportion of cells and extracellular fluid may completely mask changes or lack of change in the cells themselves. Therefore, it seems imperative that gross tissue data be interpreted in histochemical terms.

This report supplies chemical data on the liver, brain, and renal cortex of rats of various ages, including some of extreme age and some which were retarded in growth by caloric restriction. These data have been interpreted histochemically, as in the case of muscle, and are believed to provide for the liver and brain at least a first approximation of the relative cell mass and the concentration in these cells of water, three major phosphorus fractions, and the major inorganic cations. Although data on the renal cortex lend themselves less readily to histochemical analysis, a rational interpretation of the findings is given with the aid of certain additional assumptions.

The data to be presented support the suggestion, made earlier (8), that in aging there may be changes, even pronounced changes, in the organization of a tissue and the proportion of its several phases, but that the cells themselves undergo relatively minor changes in composition.

MATERIALS, METHODS, AND CALCULATION

The tissues were obtained from the rats previously described (9). Precautions were taken to prevent evaporation of moisture

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during excision of the samples. As much blood as possible was removed from the heart before the circulation had ceased. One desirable consequence of this was to reduce the blood content of the tissues, particularly that of the liver. A total of about 90 rats was used. The normally fed rats were divided in seven groups with average ages ranging from 60 to 988 days. In addition, there were two groups of animals retarded by caloric restriction which averaged 600 and 750 days of age. Many of the tissues, including those from the retarded rats, were obtained from the Laboratory of Animal Nutrition at Cornell University.

The analytical methods have been in large part described previously (9). Additional procedures, specifically the methods used for sodium, calcium, and magnesium, as well as some further analytical details are given in the appendix.

The calculations used to obtain histochemical information are the same in principle as those used for skeletal muscle (9). However, each tissue presents special problems, which made it appear desirable to change somewhat the assumptions on which the histochemical calculations were to be based. These assumptions are discussed with the data for the individual tissues. Illustrative calculations are given in the appendix.

Results

The data for liver, brain, and renal cortex are presented in three separate sections. Each section is in turn divided into two parts. The first contains the original data and the second gives the derived data, which represent a histochemical interpretation of the results. The mean values for each age group are given in tables 1 through 7, together with the standard deviation of the mean (standard error). This permits the ready estimation of the statistical significance of differences between groups. Unless otherwise specified a statistically significant difference will be taken to mean a difference for which the probability is less then 0.05 that it arose by chance. It is difficult to be sure in all cases that the only variable concerned has been age alone, since the oldest and youngest animals differ in age by approximately three years, during which time there might have been opportunity for extraneous factors to produce effects. Therefore small differences, even though significant statistically, may not necessarily be attributable to age.

TABLE 1. MEAN VALUES FOR LIVER; ORIGINAL DATA

The values are reported per kilo of serum or of blood-free, fat-free tissue. Bold type indicates significant difference ($P \leq .05$) from the starred group (*) in each section.

Group		Age in Days	No. of Rats	Weight (gm.)	Serum			Liver											
					H_2O (gm.)	Cl (mEq.)	Na (mEq.)	H_2O (gm.)	Fat (gm.)	Collagen plus Elastin (gm.)	Cl (mEq.)	Acid Sol. P (mM)	Lipid P (mM)	Residual P (mM)	Total P (mM)	Na (mEq.)	K (mEq.)	Ca (mEq.)	Mg (mEq.)	Total Base (mEq.)
								Yale-Cornell Strain											
1		60	6	111	926	101.8	138.2	750	**43**	3	**32.4**	46.0	**40.3**	30.2	119.8					
	S.E.				*1*	*1.4*	*2.1*	*2*	*2*	*1*	*0.6*	*1.1*	*1.1*	*1.2*	*3.5*					
2*		603	46	308	921	100.3	141.5	759	49	3	30.1	46.5	35.4	30.8	113.2	27.0	102.5	2.3	20.0	151.8
	S.E.				*1*	*1.0*	*0.9*	*3*	*1.3*	*0.4*	*0.5*	*2.8*	*0.4*	*3.2*	*2.6*	*0.5*	*0.4*	*0.2*	*0.3*	*0.5*
3		988	7	244	918	97.0	137.6	756	**42**	2	27.3	43.4	36.3	33.4	113.2	26.3	103.2	2.1	20.6	152.2
	S.E.				*2*	*1.4*	*1.0*	*4*	*2.5*	*0.3*	*1.4*	*1.1*	*0.8*	*1.4*	*2.0*	*0.6*	*1.0*	*0.1*	*1.2*	*1.0*
								Wistar Strain											
4		153	8	272	928	98.0	143.5													
	S.E.				*1*	*0.9*	*1.3*													
5		449	4	365	920	94.9	136.0	744	41	5	27.5				124.4					
	S.E.				*2*	*1.2*	*1.0*	*3*	*2*	*1*	*1.4*				*2.7*					
6		668	7	310	918	92.7	136.5	751	38	6	27.5				118.7					
	S.E.				*3*	*1.3*	*0.3*	*6*	*1*	*1*	*0.8*				*2.3*					
								Yale-Cornell Retarded											
7*†		610	7	328	921	100.3	141.5	751	59	6	32.7	45.9			118.1		94.6			
	S.E.				*1*	*1.0*	*0.9*	*2*	*3*	*1*	*1.0*	*1.6*			*0.6*		*2.3*			
8		611	10	104	[922]‡	[105]‡	[138]‡	**732**	**43**	7	33.2	**50.6**			**125.4**					
	S.E.							*3*	*2*	*0.7*	*0.2*	*0.4*			*1.3*					
9		752	10	121	922	105.2	138.1	**735**	**51**	4	32.6	45.6	43.0	35.0	**123.5**		**102.2**			
	S.E.				*1*	*0.9*	*0.7*	*2*	*1*	*0.2*	*1.2*	*0.8*	*0.6*	*1.0*	*1.2*		*1.2*			

† Special control group for retarded series.
‡ Assumed values.

S.E. Standard error of the mean = $\sqrt{\frac{\Sigma\Delta^2}{N(N-1)}}$

Liver.—Original Data. The values have been calculated on a blood-free, fat-free basis. The liver is particularly apt to contain large and variable amounts of blood, which could readily distort the data unless due corrections were made. The same is true to a certain extent for fat, although in none of these animals were there serious differences in fat content, such as occur under certain abnormal conditions.

There proved to be remarkably little difference in the analytical data for the various age groups (table 1). The livers of the 60 day old group of Yale rats had significantly more lipid phosphorus and less fat than the 600 day old group. In the 60 day group there also was a slightly higher chloride content, but no other significant differences were observed. Furthermore, no significant differences for any item except fat were found between the 600 and 988 day Yale groups, or between the 450 and 680 day Wistar rats. Retardation, however, resulted in significant decreases in water content and fat, and increases in total phosphorus and potassium.

Histochemical Data. From the original data it is possible to derive information as to the composition of the cells of the liver. It is assumed that the blood-free, fat-free liver is composed of (a) cells of uniform composition plus (b) extracellular fluid, E, having the same composition as blood serum, plus (c) collagen and elastin. Together, b and c are considered as the total extracellular mass, E_T. Drinker and Yoffey (10) found that liver lymph is indistinguishable from blood serum, and they hold that lymph has the same composition as the extracellular fluid of the tissue from which it derives. In contrast to liver, the extracellular fluid of muscle, as the result of similar reasoning, is usually considered to be a serum ultrafiltrate.

The ratio of chloride to sodium is greater in liver than in serum as Fenn (11) and Manery and Bale (12) have previously ob-

TABLE 2. MEAN VALUES FOR LIVER; DERIVED DATA

E_T and C calculated per kilo fat-free tissue; other values per kilo cell water. Bold type indicates significant difference ($P \leq .05$) from starred group (*) of each section.

Group	Age in Days	No. of Rats	Weight (gm.)	E_T (gm.)	C (gm.)	$(H_2O)_c$ (gm.)	$[ASP]_c$ (mM)	$[LP]_c$ (mM)	$[RP]_c$ (mM)	$[TP]_c$ (mM)	$[K]_c$ (mEq.)	$[Mg]_c$ (mEq.)	$[Ca]_c$ (mEq.)	$[TB]_c$ (mEq.)
Yale-Cornell Strain														
1	60	6	111	**219**	**781**	**704**	82	**73**	55	210				
S.E.				*4*	*4*	*3*	*2.5*	*2.4*	*2.0*	*4*				
2*	603	46	308	197	803	724	80	61	53	194	175	33	2.4	210
S.E.				*4*	*4*	*4*	*4.1*	*1.6*	*5.8*	*6*	*2*	*1*	*.3*	*3*
3	988	7	244	211	789	715	76	64	60	200	178	34	1.9	214
S.E.				*17*	*17*	*5*	*2.9*	*1.9*	*3.9*	*8*	*2*	*1*	*.1*	2
Wistar Strain														
5*	449	4	365	182	818	709				212				
S.E.				*17*	*17*	*4*				*5*				
6	668	7	310	190	810	713				203				
S.E.				*9*	*9*	*7*				*4*				
Yale-Cornell Retarded														
7*	610	7	328	233	767	708	84			221	178			
S.E.				*13*	*13*	*4*	*4.6*			*3*	*5*			
8	611	10	104	232	768	**683**	**96**			**237**				
S.E.				*9*	*9*	*4*	*1.8*			*5*				
9	752	10	121	195	805	**683**	83	78	67	228	185			
S.E.				*14*	*14*	*6*	*2.5*	*2.4*	*2.2*	*7*	*5*			

Symbols: E_T = Total extracellular phase; C = total cellular phase; ASP = acid soluble phosphorus; LP = lipid phosphorus; RP = residual phosphorus (acid insoluble-nonlipid); TP = total phosphorus; TB = total base.

served. The excess chloride is presumably intracellular. On the assumption that all of the sodium is extracellular, the concentration of intracellular chloride was calculated for the large group of 600 day rats. The value obtained, 13 m-Mol† per kilo of cells, was assumed to be the same for the other groups, and on this basis appropriate deduction was made from the total chloride in the calculation of the extracellular mass (see also appendix). Since the comparison of most concern for this report is between the 600 and 988 day groups, sodium data were obtained for these groups and were used directly for the calculation of the extracellular mass.

There was found to be a somewhat greater cell mass and cell water concentration and a lesser cell concentration of lipid phosphorus in the large 600 day group (no. 2) than in the 60 day group (table 2). Although these differences are statistically significant they are probably not associated with aging, since group 7, also 600 days of age, did not show them. In the oldest group (no. 3) the only significant change compared to group 2 (600 day) was a slight decrease in the chloride concentration of the cells as compared to the 600 day groups (8.9 ± 0.8 compared to 13.2 ± 0.4 m-Mol per kilo of cells—not shown in the table). Retardation resulted only in a moderate decrease in cell water concentration, and, in the case of the younger retarded groups, an increased acid-soluble phosphorus and total phosphorus concentration.

Thus, in the liver of the rat, even in extreme age, no pronounced changes were observed in either the proportion of the cellular and extracellular compartments or in the composition of the cells. This relative constancy of cell composition may not, of course, extend to all cell constituents, but it does suggest the tentative thesis that the liver in the rat is not seriously affected by aging. This would be quite reasonable since the hepatic cells are capable of cell division throughout life.

TABLE 3. BRAIN (CEREBRUM); ORIGINAL DATA

Values are reported per kilo of total tissue (not fat-free). Bold type indicates significant difference ($P \leq .05$) from the starred group (*) of each section. Serum data are given in table 1.

Group	Age in Days	No. of Rats	H_2O (gm.)	Fat (gm.)	Collagen plus Elastin (gm.)	Cl (mEq.)	ASP (mM)	LP (mM)	RP (mM)	Total P (mM)	K (mEq.)	Na (mEq.)	Ca (mEq.)	Mg (mEq.)
Yale-Cornell Strain														
1	60	2	**800**	**76**		33.9	33.2	50.8	13.7	97.7	100.8			
2*	603	46	773	96		34.6	33.2	56.4	16.4	106.0	99.3	45.7	4.0	13.5
S.E.			*0.8*	*0.9*		*0.6*	*0.5*	*0.3*	*0.4*	*0.5*	*2.0*	*0.4*	*0.8*	*0.9*
3	988	7	770	**87**		34.2	**31.9**	54.3	16.4	**102.6**	**94.3**	**51.4**	3.3	12.4
S.E.			*1.2*	*1.1*		*0.4*	*0.1*	*1.4*	*0.2*	*1.5*	*0.3*	*0.5*	*0.4*	*0.9*
Wistar Strain														
4	153	7	**786**	89	5	34.7				**96.2**	99.4			
S.E.			*1.5*	*0.9*	*1.4*	*0.5*				*2.1*	*2.6*			
5*	449	5	778	89	6	33.0				104.0	98.7			
S.E.			*2.4*	*1.6*	*0.5*	*1.2*				*0.8*	*1.5*			
6	668	7	777	89	6	31.3				103.9	98.5			
S.E.			*2.0*	*0.6*	*1.0*	*0.6*				*1.5*	*2.0*			

S.E. =Standard error of the mean.

† m-Mol—Abbreviation for millimol.

Brain (Cerebrum).—Original Data. These data (table 3) are purposely not corrected for fat. The brain lipids are a fundamental part of brain structure and in the adult represent a constant proportion of the brain mass. Hence there is no necessity for calculating on a fat-free basis as there is in the case of muscle, skin, liver, etc. Insufficient blood

was found in the brain samples to warrant calculation on a blood-free basis.

In general, there were even fewer changes observed in the brain (table 3) than in the liver. Yannet and Darrow (6) have reported that adult cat brains contain less water and more fat and phosphorus than young brains. Similar differences are seen to exist between young and adult rat brains (groups 1 and 4 compared with groups 2 and 5 respectively). In extreme age (group 3) small decreases were observed in fat, acid-soluble phosphorus, and potassium, and an increase in sodium was found.

most of the fat, and a fluid phase consisting of the remaining extracellular fluid in the interstices. However, present data and rationale do not permit histochemical separation of these two phases.

No significant differences were found between the brains of the Wistar rats of different ages (table 4). For the oldest Yale groups there was a significant decrease in cell water concentration, a rise in cell sodium, and a barely significant fall in cell potassium.

The total base values, obtained by summation, did not change. If the calculations

TABLE 4. BRAIN (CEREBRUM); DERIVED DATA

E_T, C, fat and phospholipid are calculated per kilo of total tissue; other values per kilo of cell water. Figures in bold type differ significantly ($P \leq 0.05$) from values for starred group (*) of each section.

Group	Age in Days	No. of Rats	E_T (gm.)	C (gm.)	Total Fat (gm.)	Phospholipid (as Lecithin)† (gm.)	$(H_2O)_c$ (gm.)	$[ASP]_c$ (mM)	$[RP]_c$ (mM)	$[Na]_c$ (mEq.)	$[K]_c$ (mEq.)	$[Ca]_c$ (mEq.)	$[Mg]_c$ (mEq.)	$[TB]_c$ (mEq.)
Yale-Cornell Strain														
1	60	2	302	622	**76**	40	**809**	64	27		198			
2*	603	46	310	594	96	44	790	69	35	5	209	7	28	249
S.E.			*5.5*	*5.7*	*0.9*	*0.8*	*1.7*	*1.6*	*0.5*	*1.1*	*2.3*	*1.8*	*2*	
3	988	7	315	598	**87**	43	**772**	67	36	**16**	**198**	5	26	245
S.E.			*4.6*	*3.8*	*1.1*	*1.1*	*4.9*	*0.8*	*0.9*	*2.1*	*4*	*1*	*0.4*	
Wistar Strain														
4	153	7	326	585	89		801				210			
S.E.			*3.5*	*4.3*	*0.9*		*2.3*				*7*			
5*	449	5	313	598	89		794				206			
S.E.			*11*	*10*	*1.6*		*4*				*6.9*			
6	668	7	305	606	89		794				200			
S.E.			*4.8*	*5.3*	*0.6*		*4*				*4.4*			

For meaning of the symbols see table 2.
† Lipid phosphorus ×.789.

In contrast with the rat cerebrum, human brain was found by Strobel (13) to increase in water content in senescence.

Derived Data. The calculation of extracellular fluid, E, is based on the chloride content of the brain, using the same assumptions made in regard to skeletal muscle (9). The brain is divided into three parts: the extracellular fluid plus collagen and elastin, E_T, the cellular mass, C, and the total fat. The extracellular compartment actually consists of two major histologic phases, a myelin phase which contains some of the extracellular fluid and

are correct, the total base concentration is 50 per cent higher per kilo of cell water than it is per kilo of serum water. Some of this total base, here assigned to the cells, may actually be associated with phospholipid in the myelin sheaths. Christensen and Hastings (14) have shown that phospholipids are combined with a relatively large amount of base. Direct microanalysis of myelin would be of considerable interest.

Renal Cortex.—The renal capsule was removed and the cortex was separated as thoroughly as possible from the medulla for analysis.

Original Data. These values are corrected for the observed blood content but are not calculated on a fat-free basis, since, as in the case of brain, the total fat is a relatively constant and presumably functional component of the kidney. The fat of the renal cortex is apparently almost entirely intracellular.

In contrast to liver and brain, aging in the kidney is accompanied by large changes in almost all substances measured (table 5). With advancing age, there was found to be a marked increase in water, collagen plus elastin, chloride, and sodium, and a decrease in all of the phosphorus fractions and potassium. These changes were observed in both Wistar and Yale strains and were clearly evident in the middle-aged 449 day old groups. In passing from 603 days (group 2) to 988 days (group 3) there were further changes in the same direction, most of which were significant. Especially prominent was an increase in collagen plus elastin. These changes may not be an inevitable consequence of aging, since group 7 (610 days) displayed a chemical pattern much closer to that of the youngest group than to the other 600 day old group. Thus the water content is about the same in group 7 and group 1 (60 days), and the total phosphorus and potassium values are only moderately decreased. Group 7 was on a special control diet for the retardation experiments, which may have been more favorable to the welfare of the kidney. The kidney of the rat is an organ that seems to be particularly susceptible to damage. Furthermore, at a given age there is a marked individual difference in the degree of pathologic change, even on the same dietary regime.

Simms and Stolman (15) have reported

TABLE 5. RENAL CORTEX; ORIGINAL DATA

Values are reported per kilo of blood-free tissue (not fat-free). Figures in bold type differ significantly ($P \leq 0.05$) from values for starred group (*) of each section. Serum data are given in table 1.

Group	Age in Days	No. of Rats	H_2O (gm.)	Fat (gm.)	Collagen plus Elastin (gm.)	Cl (mEq.)	Acid Sol. P (mM)	Lipid P (mM)	Residual P (mM)	Total P (mM)	K (mEq.)	Na (mEq.)	Ca (mEq.)
Yale-Cornell Strain													
1	60	6	**738**	**44**	**7**	**46.2**	**39.7**	**36.8**	**26.1**	**102.6**	**72.4**		
S.E.			*1.5*	*2.4*	*1*	*1.8*	*1.1*	*0.9*	*0.5*	*1.6*	*1.2*		
2*	603	46	779	40	11	54.0	32.5	26.6	21.6	80.7	62.9	75.6	4.8
S.E.			*2*	*1.3*	*1.4*	*1.4*	*1.1*	*1.6*	*0.3*	*2.3*	*0.6*	*2.6*	*0.6*
3	988	7	783	**32**	**17**	59.0	**28.8**	24.2	20.6	**73.5**	**54.2**	**88.0**	**3.1**
S.E.			*4*	*1.2*	*2.5*	*2.0*	*1.1*	*1.3*	*0.6*	*2.5*	*1.5*	*5.3*	*0.4*
Wistar Strain													
4	153	8	**750**		**6**	**44.6**				**99.6**	**78.9**	**61.4**	
S.E.			*1.8*		*0.3*	*1.6*				*1.4*	*1.2*	*1.4*	
5*	449	5	765		8	**44.0**				88.2	63.5		
S.E.			*1.4*		*0.9*	*3.6*				*0.8*	*2.0*		
6	668	6	765		11	**51.0**				86.6	67.1		
S.E.			*1.3*		*1.0*	*2.2*				*1.7*	*2.0*		
Yale-Cornell Retarded													
7*†	610	7	736		11	49.4	39.5			94.0	69.4		
S.E.			*6.7*		*0.7*	*2.0*	*2.0*			*1.9*	*1.6*		
8	611	10	**718**	**45**	9	53.8	**47.1**			**100.6**			
S.E.			*2.0*	*2.1*	*0.8*	*1.6*	*1.8*			*0.3*			
9	752	10	736	**45**	10	**57.6**	35.5	34.3	23.8	93.6	**62.1**		
S.E.			*3*	*0.8*	*0.6*	*0.8*	*0.6*	*0.4*	*0.4*	*1.0*	*1.3*		

† Special control group for retardation experiment.

data on the human kidney in senescence. They found changes similar to those reported here for the rat, but of a lesser magnitude. Eichelberger and Bibler (16) studied the electrolyte changes in hydronephrotic whole dog kidneys and observed a marked increase in water content, but potassium, sodium, and chloride were unchanged. The type of renal damage was quite different from that which is found in the aged rat.

stacles to the utilization of gross tissue data to provide a description of the renal cortex in histochemical terms. It seems probable that the kidney, which absorbs both sodium and chloride from the glomerular filtrate, would contain significant intracellular concentrations of these ions. If this be true, it is not permissible to base the calculation of the extracellular fluid on the total chloride or sodium content. Indeed, if calculations are made assuming that all of either ion is

TABLE 6. RENAL CORTEX; DERIVED DATA

E+U, and C are calculated per kilo blood-free tissue, $(C+E)_{EU}$ is calculated per kilo E+U, $(Fat)_c$ and $(P.\ Lip.)_c$ are calculated per kilo of cells; the other values are calculated per kilo cell water. Figures in bold type differ significantly ($P \leq 0.05$) from values for starred group (*) of each section.

Group	Age in Days	No. of Rats	E+U (gm.)	C (gm.)	$(C+E)_{EU}$ (gm.)	$(Fat)_c$ (gm.)	$(P.\ Lip.)_c$† (gm.)	$[Cl]_c$ (mEq.)	$[ASP]_c$ (mM)	$[LP]_c$ (mM)	$[RP]_c$ (mM)	$[TP]_c$ (mM)	$[K]_c$ (mEq.)	$[Na]_c$ (mEq.)	$[Ca]_c$ (mEq.)
Yale-Cornell Strain															
1	60	6	**280**	**720**	24	62	40	**32**	83	78	56	217	153		
S.E.			*4*	*4*	*4.3*	*4*	*2.5*	*5*	*2.7*	*5*	*1.3*	*4.1*	*4.2*		
2*	603	46	413	587	26	69	35	19	82	69	57	208	160	47	10
S.E.			*13*	*13*	*3.0*	*0.7*	*1.3*	*3.0*	*2.1*	*2.5*	*0.8*	*2.4*	*3.5*	*1.8*	*1.5*
3	988	7	441	550	**37**	**57**	34	25	76	67	57	200	**145**	66	4
S.E.			*14*	*14*	*3.7*	*2.1*	*1.1*	*4.7*	*2.5*	*2.2*	*1.4*	*2.6*	*1.9*	*13*	*1.5*
Wistar Strain															
4	153	8	**311**	**689**	18			23				**220**	**173**	37	
S.E.			*5*	*5*	*1.0*			*4.5*				*2.7*	*2.0*	*3.5*	
5*	449	5	362	638	23			12				211	150		
S.E.			*6*	*6*	*2.0*			*7.0*				*1.7*	*4.9*		
6	668	6	382	618	30			26				213	164		
S.E.			*10*	*10*	*3.5*			*4.6*				*3.6*	*4.8*		
Yale-Cornell Retarded															
7*	610	7	288	712	41			37	84			201	149		
S.E.			*19*	*19*	*4.2*			*3.0*	*3.0*			*3.3*	*3.6*		
8	611	10	**227**	**773**	41	63		**58**	93			199			
S.E.			*6*	*6*	*3.5*	*3.2*		*3.0*	*3.6*			*1.6*			
9	752	10	284	716	35	62	38	**52**	**75**	74	51	200	**131**		
S.E.			*9*	*9*	*1.6*	*1.6*	*0.7*	*2.1*	*1.3*	*1.4*	*1.1*	*3*	*2.5*		

† Phospholipid calculated as lecithin from the lipid phosphorus (LP ×.789).

Caloric restriction (groups 8 and 9) appears to delay the development of the renal changes. Thus the 750 day old retarded group (no. 9) was comparable to the 600 day old control group except for a decreased potassium and increased chloride content. The higher chloride values were observed in both retarded groups, and the water content of the 600 day old retarded group was lower than for any other group.

Derived Data. There are several ob-

extracellular, the calculated cell water concentrations appear to be unreasonably low (17). Furthermore, the blood-free kidney consists of cells, urine, and a nonurine-extracellular phase. The urine has a different composition in different parts of the tubular system and in general must differ from the nonurine-extracellular fluid. Although it follows that a completely satisfactory solution cannot be made without more information, it was found that the

introduction of two simplifying assumptions permitted the calculation of tentative histochemical data which rationalized the changes with age in the renal cortex in a useful manner.

The first assumption is that the cell water concentration is constant at a level of 650 gm. per kilo of cells (not fat-free). This is the equivalent of about 700 gm. of water per kilo of cells on a fat-free basis, which is approximately equal to the value found for the cells of the liver. This assumption is in accord with the finding that the cell water concentration changes little with age in either liver, brain, skeletal or cardiac muscle. The second assumption is that all of the extracellular fluid including the urine is equivalent to a serum ultrafiltrate. This is based on the belief that the amount of concentrated urine in the distal convoluted tubules is small enough not to jeopardize the results. If this assumption is wrong, the chief consequence would be to give somewhat too high values for intracellular chloride and sodium.

The results (table 6) seem to justify the foregoing assumptions. The cortex of the oldest kidneys appeared to contain a cell mass only about 75 per cent of that of the youngest kidneys. However, the remaining cells showed relatively little change in composition. In the older kidneys no significant changes were found in the cell concentrations of fat (or phospholipid), or any of the three phosphorus fractions. Small changes in the potassium concentrations were observed. The cell concentrations of chloride and sodium were quite variable, as might be anticipated. The same was true for calcium, which perhaps has been erroneously assigned to the cells, since the kidney is prone to the deposition of calcium (outside of the cells). Retardation seemed to prevent the loss in the proportion of cells or even to increase the relative cell mass. Both retarded groups had relatively large concentrations of intracellular chloride. There was a significant increase in the extracellular concentration of collagen plus elastin in the oldest group (no. 3).

The calculated cell concentrations of the three phosphorus fractions were remarkably similar in the liver and kidney, whereas the potassium concentration was definitely lower in the kidney. This latter may be the consequence of the prominent concentrations of sodium in the renal cells.

TABLE 7. HISTOCHEMICAL DATA FOR FIVE RAT TISSUES AT 600 DAYS OF AGE
See tables 2 and 6 for explanation of the symbols.

	E_T (gm.)	C (gm.)	$(C+E)_E$ (gm.)	$(H_2O)_c$ (gm.)	$[Cl]_c$ (mEq.)	$[ASP]_c$ (mM)	$[LP]_c$ (mM)	$[RP]_c$ (mM)	$[TP]_c$ (mM)	$[K]_c$ (mEq.)	$[Mg]_c$ (mEq.)	$[Na]_c$ (mEq.)	$[Ca]_c$ (mEq.)	$[TB]_c$ (mEq.)
Skeletal muscle	123	877	68	743	[0]	98	14	5	117	170	38	7	4	219
Cardiac muscle	249	751	38	735	[0]	67	41	21	130	143	32	11	3	189
Liver	197	803	15	724	18	80	61	53	194	175	33	[0]	2	210
Renal cortex	413	587	26	[700]	19	82	69	57	208	160		47	10	
Brain (Cerebrum)	310	594	15	790	[0]	69		35		209	28	5	7	249
Serum				921	120	3	1	0	4	4	3	154	5	166

Comparison Between Different Rat Tissues.—In view of the apparent relative constancy of the intracellular environment throughout the life of the rat, it may be of interest to compare the histochemical data at 600 days of age in the five tissues studied (table 7). Blood serum is included for contrast. Some of the data for skeletal and cardiac muscle have not been published previously. The cell mass varies from a maximum of nearly 900 gm. per kilo in skeletal muscle (1) to a minimum of 600 gm. per kilo in brain tissue. The value of C for renal cortex is not representative of the normal organ (see under Renal Cortex). The highest concentration of collagen and elastin per kilo of extracellular fluid is encountered in muscle (68 gm. per kilo) and the lowest, in liver and brain (15 gm. per kilo). The cell water concentration is greatest in brain (790 gm. per kilo), lowest

in liver (724 gm. per kilo). The concentrations in the cell water of the three phosphorus fractions are nearly identical in liver and kidney. The three fractions combine to give the imposing total of about 200 m-Mol per kilo of cell water. The corresponding figure for skeletal muscle is only 117 m-Mol. The acid-soluble phosphorus concentration is greatest in skeletal muscle fibers (98 m-Mol per kilo of water) and lowest in cardiac fibers and brain cells (about 70 m-Mol per kilo of water).

The potassium concentration is about the same in liver cell and muscle fiber. It is higher in the brain and lower in cardiac muscle fibers. A possible explanation for the higher value in the brain has already been commented upon. The lower figure in the kidney may be due to the presence of a considerable concentration of intracellular sodium. The total base values are all much larger in the tissue cells than in serum (166 mEq.* per kilo of water). This is understandable, since the major portion of the intracellular anion is multivalent (organic phosphate compounds and protein), and a substantial portion of the intracellular cation is magnesium, which is divalent and possibly only in part dissociated. Therefore in order to maintain osmotic equilibrium there must be a greater total base concentration in the cell than out.

Discussion

Data for five rat tissues have now been presented in this series of reports on histochemical changes in aging (1, 18). In two tissues, skeletal muscle and renal cortex, aging was attended by marked increases in the extracellular phase at the expense of the cellular mass. In a third, cardiac muscle, there was a moderate increase in the extracellular phase. In the remaining two tissues, liver and brain, little or no changes in the proportion of extracellular to intracellular mass were observed. In none of the five tissues were marked changes found in the composition of cellular phase. Indeed, it seems probable that no changes of major functional importance occurred in the cellular concentration of any of the materials measured, since much greater changes in many of these materials have been produced experimentally without undue distortion of function. Thus the water concentration of cells may be changed over much wider limits than here described, by dehydration or by the injection of hypotonic solutions (19). Nearly half of the muscle fiber potassium may be replaced by sodium through the use of diets deficient in potassium with only moderate functional consequences (20). On various experimental diets the lipid phosphorus of the liver may be reduced by an amount greatly exceeding the limits established by the present data on aged tissues. Actual death of tissues results in changes in cell composition of an even greater order of magnitude. Dying muscle (5, 21) and liver cells (22) equilibrated with Ringer's solution lose nearly all of their potassium, magnesium, and acid-soluble phosphorus, and absorb large amounts of water, sodium, and chloride. The data indicate that no large numbers of such cells were present in the aged tissues.

Only the major cell constituents have been measured in the aged rat tissues. It is conceivable that other vital materials present in much smaller concentration may be seriously disturbed in aging, but until such time as these substances are measured the hypothesis must be accepted that functional changes in aging are attributable to loss of functioning cells and changes in tissue architecture rather than to alteration in the metabolic capacities of the individual cells.

Summary

1. The liver, brain, and renal cortex of young, adult, and aged rats were analyzed for fat, collagen plus elastin, chloride, sodium, potassium, calcium, magnesium, acid-soluble phosphorus, lipid phosphorus, and residual (acid-insoluble, nonlipid) phosphorus.

2. The data have been utilized to furnish a histochemical description of these tissues.

* mEq.—Abbreviation for milliequivalent.

3. Only moderate changes were found either in the gross composition of the liver or in the composition of the cells themselves.

4. During senescence, the composition of the brain underwent almost no observed change.

5. Senescence in the kidney resulted in pronounced changes in gross composition, which seemed to be the consequence of a large decrease in the relative mass of cells without much change in the composition of the remaining cells.

6. The effects of retardation of growth by caloric restriction were also observed. The findings suggest that retardation protects the kidney from the changes otherwise associated with aging.

Appendix

Methods

The methods used for the measurement of blood, collagen, elastin, chloride, total phosphorus, and potassium have been previously described (9).

Acid-soluble Phosphorus. This was determined in extracts prepared with 0.75N nitric acid. Nitric acid has been shown to be very comparable to trichloracetic acid as an extractant (9).

Total Lipids. To measure the total lipids, the washed, acid-insoluble residue was extracted with cold alcohol, boiling alcohol, and finally ether. The extracts were combined, evaporated, and heated at 100 C. *in vacuo* to constant weight.

Lipid Phosporus. The lipid phosphorus was measured on these extracted lipids.

Residual Phosphorus. The residual phosphorus was measured on the residue left after the extraction with organic solvents. The Fiske and Subbarow reagents (23) were used for all of the phosphorus determinations.

Sodium, Calcium, and Magnesium. Sodium, calcium, and magnesium were determined in nitric acid tissue extracts. The extracts were dry ashed as described for potassium (9). It was found that sodium could be measured without removal of phosphate by precipitation as the zinc uranyl acetate. The uranyl ion in an aqueous extract of the precipitate was determined by a colorimetric method. The ashed samples were transferred to centrifuge tubes, dissolved in 0.25 ml.* water per gram of tissue, and precipitated with 20 ml. of the reagent of Barber and Kolthoff (24) per gram of tissue. The precipitate was washed once with glacial acetic acid containing 2 per cent of the Kolthoff reagent and saturated with sodium zinc uranyl acetate. It was washed a second time with 95 per cent ethyl alcohol, to which had been added 10 per cent of the first wash and 10 per cent of acetic acid. This wash was likewise saturated with sodium zinc uranyl acetate. The dried precipitate was stirred with 10 ml. water to dissolve the sodium triple salt and centrifuged to remove the insoluble uranyl phosphate. Aliquots (0.1 to 0.2 ml.) were mixed with 25 ml. of 50 per cent acetic acid containing 0.1 per cent ascorbic acid, following which 0.5 ml. of fresh 25 per cent potassium ferrocyanide was added. After ten minutes the samples were read colorimetrically against standards prepared from known sodium zinc uranyl acetate solutions. A Wratten filter no. 45A in the eyepiece increased the precision of reading (transmission maximum, about 480 mμ†). Ferrocyanide gives an intense brown color with the uranyl ion. However, the reagent has never been popular because it frequently becomes turbid. This may be controlled through the use of 50 per cent acetic acid, but this acidity accelerates the oxidation of ferrocyanide, which results in the formation of blue ferro-ferricyanide. The addition of ascorbic acid prevents this oxidation, and the resultant solutions yield a stable brown color which is proportional to the uranyl concentration. The color increases only about 4 per cent between ten minutes and two hours after the addition of the ferrocyanide. This reagent would be applicable to the measurement of exceedingly minute quantities of sodium, since satisfactory readings may be obtained with an

* ml.—Abbreviation for milliliter.

† mμ—Abbreviation for millimicron.

amount of uranyl salt equivalent to 0.2 μg.* sodium per milliliter. It is not permissible to have a phosphate concentration that is too great during the sodium precipitation, as the results become irregular. At the dilutions used for the tissue analyses, phosphate did not appear to interfere, and equivalent synthetic salt mixtures could be analyzed, by the procedure outlined, with an accuracy of from 2 to 5 per cent, depending on the sodium concentration.

Calcium. Calcium was determined by a micromodification of the procedure of Fiske and Logan (25). Precipitation was carried out in centrifuge tubes, and the calcium oxalate was converted to the carbonate instead of to the oxide.

Magnesium. This was precipitated as the ammonium phosphate in the supernatant from the calcium precipitation and was determined on the basis of the phosphate contained in the precipitate.

Calculations

Liver. The extracellular fluid, E, was calculated on the assumption that the extracellular fluid of liver is serum and that the cells contain 13 m-Mol of chloride per kilo. It is also assumed that serum contains 85 gm. of solids per kilo. If Cl_T = tissue chloride concentration, and Cl_S = serum chloride concentration, $E = \frac{1000\ (Cl_T - 13)}{Cl_S - 13}$. [Since $1000\ Cl_T = E \times Cl_S +$ cells per kilo $\times 13 = E \times Cl_S + 13(1000 - E)$.] For example, if $Cl_S = 100$, $Cl_T = 30$, collagen plus elastin $= 3$, fat-free solids $= 240$ gm. per kilo, then $E = \frac{1000(30 - 13)}{100 - 13} = 195$, $E_T = 198$, and $C =$ 802 gm. per kilo of tissue. The solids of $E_T = 3 + .195 \times 85 = 20$, therefore the solids of $C = 240 - 20 = 220$ and the water content of $C = \frac{802 - 220}{.802} = 726$ gm. per kilo, etc. If it were assumed instead that all of the chloride is extracellular, the above data would lead to a value of 303 for E_T and a value of 697 for the cell water content. Finally, if it were assumed that all of the tissue chloride is extracellular but present in a serum ultrafiltrate, these same data would lead to a value of 273 for E_T and a value of 678 for the cell water content, an unreasonably low figure.

Kidney. It was assumed that the cells contain 350 gm. of total solids per kilo (not fat-free), and that the extracellular fluid and urine are serum ultrafiltrates (with 10 gm. of solids per kilo). If E + U = the sum of extracellular fluid plus urine, C = mass of cells per kilo, CE = collagen plus elastin, and S = total solids per kilo, then $C = \frac{S - CE - 10}{0.340}$. [Since, $S = .350C + .010(E + U) + CE = .350C + .010(1000 - C + CE)$.] For example, if $S = 260$ and $CE = 10$, then $C = \frac{260 - 10 - 10}{.340} = 705$ gm. cells per kilo of tissue.

* μg.—Abbreviation for microgram.

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Age and Infection—A Review

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SINCE THE EARLY DAYS OF BACTERIOLOGY IT HAS BEEN THE INFECTIOUS DISEASES OF THE YOUNG WHICH HAVE BEEN MOST FREQUENTLY STUDIED, LITTLE ATTENTION BEING PAID TO THE EXPERIMENTAL INFECTION OF THE OLD. CLINICAL OBSERVATIONS HAVE SHOWN THAT PARALLEL WITH THE PROCESS OF AGING THERE DEVELOPS AN INCREASED RESISTANCE TO INFECTION. HOWEVER, THE RESULTS OF EXPERIMENTS WITH NEOPLASTIC INFECTIONS INDICATE THAT THE RESISTANCE OF THE OLDER INDIVIDUAL DOES NOT ALWAYS RESULT IN COMPLETE SUPPRESSION BUT SOMETIMES IN MODIFICATION, OF THE INFECTION. IT IS TIME NOW TO STUDY SYSTEMATICALLY EXPERIMENTAL INFECTION OF THE OLD.

INTRODUCTION

JUST as an individual's outlook on life and its problems so changes with advancing age that he may not recognize himself as he was in the past, so also the pattern of infection can alter. Sometimes old and young persons attacked by a single infectious agent react as though old and young were of two different species, or as though they had been attacked by two different infectious agents.

The greater susceptibility of the young to acute infection was probably one of the oldest of empirical medical observations. From this observation and from the results of experimentation, the concept has emerged that there is an increasing resistance to many infectious diseases which parallels the growth and differentiation of the individual, with a possible drop in resistance in advanced old age. This concept can perhaps be expressed more precisely by stating that, in general, infection is modified by increasing age to the obvious advantage of the host. This concept holds true generally, despite those exceptions in which it is not resistance but susceptibility that is acquired by maturation and aging.

No service to the problem of an understanding of the modifications of infection by age could be greater than the exposure of the fundamental laws that are responsible for the modifications. This review represents an attempt to bring these laws to light, though it must be admitted at the start that I shall fall short of my purpose. The data available are many but are often so scattered that it is difficult or even impossible to arrange them coherently. Hypotheses may be formulated, but the perfect experiments which would prove them are always lacking. In fact, this review is more concerned with what should be done than with what has been accomplished.

RESISTANCE ACQUIRED BY THE CELL IN THE PROCESS OF AGING

To proceed systematically in an analysis of the relation of age to infection, it would seem that the first question that must be asked is: When disease is modified to the obvious advantage of the host by aging or by other means, is it the cell or the tissue that acquires the resistance? Even though a platitude is stated, in metazoans the concept of a cell cannot be dissociated from its environment, that is, the tissue. Too often the cell-parasite conflict is spoken of as if the cell were an abstract entity without a definite location.

It seems unquestionable that the most efficient form of resistance against infection would be that resulting from an inherent lack of affinity between cell and parasite or its secretions, both behaving like two inert chemicals in a test tube.

Such a form of resistance operates in some of the numerous cases of the adaptation of unicellular organisms to inorganic, organic, or biologic products exerting a

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toxic effect on them. In these cases the resistance, acquired by mutation, by selection, or by a combination of both, is transmitted to the progeny, a phenomenon which poses important medical problems. The acquisition of resistance by bacteria to sulfa drugs and to penicillin, and of pathogenic trypanosomes to arsenicals, will suffice to illustrate the point.

The experiments on the interaction between bacteriophage and bacteria, first carried out by Twort and d'Herelle and later developed by others are especially pertinent in this respect, for the following reasons: First, phage is specifically fixed by susceptible bacteria but not by nonsusceptible ones; second, bacteria originally susceptible but rendered resistant to phage do not fix it nor do the progeny; and third, aged bacteria are resistant to phage.

In view of these facts, there are two questions that must be asked: Is this type of resistance present in higher organisms? And, if the answer is in the affirmative, is the resistance acquired by aging?

Study of bacterial infections has not revealed the answer to the first question, for bacteria are too complex; they may live on what is dead and they multiply to a certain degree in animals considered as resistant. However, there are some data on poisons from bacteria or from other sources, upon which to speculate. Thus, in order to explain the resistance of several species of cold-blooded animals to some glucosides and snake venoms, it has been postulated that the tissues are endowed with a congenital insusceptibility to the poisons. The same has been stated to be true also in the case of some mammals—for example, rats and hedgehogs are resistant to several vegetable and animal toxins, and fowls and rats, to tetanus and diphtheria toxins, respectively. It has been demonstrated by MacNider (5) that in some mammals the cells that develop in the repair to the injury inflicted by simple chemical poisons are resistant to the effects of the same or other chemicals. A similar phenomenon is seen in the experiments on selective fixation of several bacterial toxins by the pulp of susceptible tissues, as exemplified in the case of the fixation of tetanus toxin by brain extracts, as was observed long ago by Takaki and Wassermann. Also, the insusceptibility of several cold-blooded animals to some viruses, such as rabies, has also been explained on the basis of a lack of affinity between virus and cells. It is clear, though, that no matter how suggestive these experiments are, they do not prove that the mechanism under review plays an important part in the natural resistance against infection.

It would seem that the problem could best be approached in the field of virus infections. Some viruses are strictly species-specific, and in very small amounts. A single unit may be capable of causing infection. Viruses have been cultivated in tissue culture in the presence of a great variety of cells, as well as in developing embryos, especially those of chickens. These properties of viruses make them the ideal tools for studying the reactions between the parasite and the cells from either susceptible or resistant animals. It is surprising to realize that it is only in the last few years that reliable experiments dealing with such a basic problem began to be available, and most of the experiments were conducted for purposes entirely unrelated to the present problem.

The experiments on the interaction between bacteria and bacteriophage have been mentioned. The work on this particu-

lar topic may be regarded as almost perfect, as is attested by the contributions of Burnet (6) and of Luria and Delbrück (7). However, comparable experiments with animal viruses are but few. All that can be quoted are the selective inactivation of the virus of the Rous sarcoma by muscle pulps from susceptible birds (8), which can be interpreted as revealing a specific fixation of the virus by the muscle cells, and a fixation of the virus of the rabbit fibroma and of vaccinia by rabbit fibroblasts from tissue cultures (9).

The experiments on growth of viruses in tissue culture can now be considered, even though no preliminary attempts were made to investigate whether these viruses were or were not specifically fixed by the cells employed. Among the numerous papers published on the subject only a few can be quoted for the purposes of this review. They show that the viruses of fowl-pox, foot-and-mouth disease, poliomyelitis, and of the Rous sarcoma multiply in the presence of cells from susceptible animals but not in the presence of cells from resistant ones. Another contribution on fowl plague tends to emphasize the necessity of a certain sort of cell from the susceptible animal if the virus is to multiply. The only worker who has approached the problem directly is Pearce (10), who has shown that virus III, pathogenic only for rabbits, can easily be cultivated in testicular cells of the rabbit but not in similar cells from the rat or guinea pig, or in whole chick embryos even if rabbit serum is added.

The experiments of Pearce, together with those already reviewed, indicate the existence of an intrinsic cellular factor in the resistance of some species to virus infection and suggest, but do not prove, that this factor is a lack of inherent affinity between virus and cell, such as is exhibited by unicellular organisms. It is obvious that much more remains to be done in this field. Many more viruses should be studied, and fixation experiments such as those carried out with bacteriophage should be performed. Study of the reactions between virus and cell before and after the virus has been adapted to a given species would be particularly desirable.

Two recent lines of research may contribute important data to the subject. One involves what is called the interference phenomenon, that is, the inhibiting effect that two viruses attacking a single host exert on each other. The other line of study is concerned with the selective effect of some viruses on certain isolated cells such as red blood cells. Study of these phenomena demands the use of systems in which purified virus is brought into contact with cells either in purified suspensions or cultivated in vitro—in other words, the use of the general methods that are advocated in this paper for the study of virus and cell effects.

An attempt will now be made to answer the second question: Is the refractory state of the cell acquired by aging? Experiments give the following answer: The virus of poliomyelitis, of foot-and-mouth disease, of abortion of mares, and of virus III do not infect chick embryo cells either in tissue culture or in the egg, and the adult chicken is resistant to all these viruses. The same is true for the fowl-pox virus inoculated in the human amnion, which in turn is grafted upon the chorio-allantoic membrane of the chick embryo (11). Man is wholly resistant to fowl-pox. It would seem, therefore, that in all these cases the resistance to infection is an inherent property of the cell and is present from the earliest phases of embryonal life.

However, in contrast with these examples, there is a large number of diseases to which the embryo is highly susceptible although the adult is totally or partially refractory. It is from experiments upon chickens that practically all the information about these diseases comes. The extensive use of the chicken embryo for virus culture has disclosed the fact that many viruses thrive in the embryo whereas they do not affect the adult individual. The viruses of influenza, yellow fever, St. Louis and Japanese encephalitis, myxoma of rabbits, and many others can be mentioned as

examples. The susceptibility of fetal guinea pigs to influenza, vaccinia, and salivary gland virus and even to the B.C.G. strain of tubercle bacillus to which adults are largely resistant is also illustrative.

Can it be postulated in these cases that the cells acquire a resistance? The following experimental results prove how unwarranted it would be to do so. As first shown by Andrewes (12), if cells of animals immune to salivary gland virus, to virus III, to herpes, and to pseudorabies are cultivated in vitro they can easily be infected by these viruses. That no infection takes place when immune serum is added to cultures of immune or normal cells has been known for a long time (Pearce, 10, for references). Also, if skin cells from human beings and from chickens immune to vaccinia and fowl-pox, respectively, are grafted on the chorio-allantoic membrane of the chick embryo, the skin cells can be easily infected with the viruses (Goodpasture, 11). The multiplication of vaccinia and virus III in tumors growing in hosts resistant to these viruses, and the susceptibility of brain tissue in immune monkeys to intracerebral injections of some neurotrophic viruses, such as that of equine encephalomyelitis, should also be noted.

It is true that, in the above examples the immunity was the result of infection and was linked with antibodies, but age resistance is also often associated with natural antibodies among other factors. To reach conclusions, it would be necessary to study in every case whether the cells of adults retain a resistance in tissue culture or after being grafted to the chorio-allantoic membrane of chicks, as demonstrated by Goodpasture (11).

However, if the possible existence of a state of cell resistance acquired by aging, or after infection, or as a result of both factors combined is accepted, there are a few experimental results perhaps compatible with the possibility. For instance, as shown by Andrewes (12), virus III, to which only rabbits are susceptible, multiplies well in tissue cultures consisting of normal rabbit serum and testicular tissue from rabbits immunized to the virus, but if immune serum is used, the growth of the virus is suppressed. On the other hand, Rivers, Haagen, and Muckenfuss (13) have shown that vaccine virus does not multiply, under the same conditions, in the corneal tissue from rabbits immunized to the virus regardless of whether normal or immune serum is added. Although the experiments were conducted on two different viruses, it is pertinent to recall that the cornea is an avascular tissue which in the process of immunization follows a rhythm of its own and manufactures local antibodies (14). It may well be that in the experiment with vaccinia a state of cell immunity is dealt with, especially in view of the fact that the rabbits used were inoculated in the cornea with the virus.

These results suggest that still another problem to be solved concerns the type of cell employed in the experiments advocated in this paper. It would be well to know whether cells directly concerned with defense against infection (such as reticuloendothelial cells and lymphocytes), taken from resistant animals, differ from other cells in individual resistance to a virus. Such simple experiments as cultivating lymph node tissue from a rabbit immune to vaccinia and studying the response to the virus have never been carried out. Such experiments could be extremely instructive.

Other facts compatible with the notion of the acquisition of cell resistance may also be considered. As shown by Francis (15), the nasal epithelium regenerating after damage caused by influenza virus may acquire, on repeated exposures to this agent, a long-lasting resistance independent of the antibody content of the blood and comparable to the resistance against chemicals, as shown by MacNider. In the field of infection caused by neurotrophic viruses, should be mentioned the refractoriness of cells from the anterior horns of the spinal cord after sectioning of the axons, and the development of constitutional barriers by the impenetrability of certain synapses or

myoneural junctions (16). The latter example is of greater interest here since it is directly related to aging. The experiments on the allergic response of cells from the spleen of tuberculous animals should also be remembered. As shown by Rich and Lewis (17), these cells in tissue culture react specifically to tuberculin, and Moen and Swift (18) have shown that the hypersensitiveness persists after several transplantations representing several generations of descendants of the original cells. The phagocytic power of macrophages from tuberculous animals for the tubercle bacillus is also known to be high when these cells are transplanted into the anterior chamber of the eye of normal rabbits (19).

In summary, from the scattered observations gathered from widely different fields it seems almost certain that a congenital refractory state of the cell is the cause of the natural resistance of some species to some infections, and it may well be that a lack of affinity between cell and parasite is the basis of the phenomenon.

As for the crucial point as to whether a cell can acquire a comparable resistance after conflict with the infectious agent, can keep it forever, or can transmit it to its descendants, it must be confessed that as little is known now as when the theories of immunity were first promulgated decades ago. Nor is it known whether the cells from the aged organism possess this resistance. Consequently, there is no solid experimental ground on which to build an explanation of the phenomenon of acquisition of resistance by the whole organism in the process of aging.

Resistance Acquired by the Whole Organism in the Process of Aging

Although there are few data concerning the problem of whether or not in the process of immunization and aging the cell itself counteracts the infection in self-defence, there are many contributions concerning the acquisition of resistance by the whole organism in the process of aging. Specialization is apparently important in the process of defense against infection as it is in other physiologic functions and, accordingly, the manifestations of defense can be arranged in four categories.

(1) Natural antibodies against a great variety of antigens develop in the growing individual, appearing during the last days of embryonic development. Examples are so numerous that it would be a long task to summarize them, as has been done by Baumgartner (4), Perla and Marmorston (1), and others. The development of antibodies with age has been demonstrated in the case of isohemagglutinins, hemagglutinins, hemolysins, antitoxins, bacterial agglutinins, antihormones, and complement (20). The sensitiveness of red cells to isoagglutinins also increases with age. However, antibodies for proteins are usually not demonstrable in normal sera. Whether some or all of these antibodies represent the result of serologic maturation or the result of subclinical infections or immunization against symbiotic microorganisms has been and still is the subject of a long controversy (3)(21)(22). The existence of natural antibodies is also of fundamental importance for explaining the development of acquired antibodies, a subject which is "still nearly as puzzling today as at the time when the phenomenon was first discovered" (Landsteiner, 21). Paralleling the curve of antibody production there is a steady modification of the physicochemical properties of the blood serum, notably the globulins. Probably the best investigations in this respect have been conducted on the blood of calves before and after the ingestion of colostrum, as first studied by Howe (23) by salting-out methods, and recently by Jameson, Alvarez-Tostado, and Sortor by electrophoretic methods (24).

(2) With advancing age there is an increasing capacity to manufacture specific antibodies. Here again examples are numerous (1, 4), the first observation dating back to the days of Metchnikoff. It is a common practice in all laboratories to immunize adult animals if good antibody-titers are desired. The work of Freund (25) is especially

clear in showing experimentally the different responses of rabbits of varying ages to typhoid bacilli, sheep red cells, and horse serum. In the virus field, the contributions of Casals on rabies virus (26) and of Morgan (27) on equine encephalomyelitic virus are particularly interesting.

(3) There is a progressive increase in the capacity of tissues to react to foreign agents and an improvement in the phagocytic function of cells paralleling the process of aging. The aging process repeats in the ontogenetic development what Metchnikoff observed in phylogenetic development, another manifestation of the recapitulation law. Since 1907, when Von Pirquet noticed that nurslings give negative tuberculin reactions, several observations have demonstrated a low or no sensitivity of nurslings or children to toxins of bacterial or other sources, or to vaccine virus. Again it was Freund (28) who gave experimental expression to these observations when he injected tuberculin into tuberculous guinea-pigs of various ages and observed the low local reactivity of the young although the systemic reactivity of the young was not impaired. Analogous observations were made on pneumococcal infections in the rabbit (29). As for the changes in phagocytic power which accompany the aging process, the observations of Becker and of Herlitz, as quoted by Baumgartner (4), show the immaturity of the reticuloendothelial system in newborn animals and infants, and the observations of Culbertson (30) show the defective phagocytic power of young rats compared to older ones.

(4) A fourth and very important principle disclosed during the last fifteen years must be added to the three factors of resistance just reviewed. This principle is concerned with the permeability of tissues, as determined by the physicochemical characteristics of the intercellular cements. The cements most important for present purposes are the "tissue fluids" of the first order in Cowdry's classification—that is, those which are subepithelial and mesenchymal but are also present in other structures such as the joints, the eyes, the cumulus oöphorus of ova, and possibly other locations (31). The broad distribution of connective tissue permits the phenomena to be described to take place in practically all organs of the body. Tissue permeability has a normal, constitutional state or tonus which can be increased by certain factors and decreased by others, and the fluctuations of permeability evolve, in parallel, changes in the degree of the infection which may have a decisive bearing on the final issue of the process (32).

The ground substance is a barrier through which, despite its viscous consistency, metabolites must move easily, probably impelled by capillary force. But as a result of this viscid consistency, the ground substance offers a pronounced resistance to penetration by foreign matter, among which infectious agents and their secretions must be included. Of the factors increasing the permeability of the connective tissues, the most important are the spreading factors, some of which have been identified with mucolytic enzymes which attack the main component of the viscid ground substance, hyaluronic acid. Of the factors affecting permeability, the age of the individual is probably the most important.

If the permeability of the skin in young and in old animals is studied by means of intradermal injection of a dye, it is found that the dye spreads over a much larger area in young than in old individuals. The differences are detectable sometimes within a few minutes after the injection. If the experiment is repeated, using a virus which produces skin lesions, such as vaccinia, the same fast spreading of the inoculum in young animals is observed, and consequently, larger lesions develop later. Indeed, the young hosts may sometimes die of generalized vaccinia. The same phenomena are observed with other infectious agents.

These events repeat under natural conditions the results observed in adult animals which have been injected in the skin, and in other tissues as well, with a variety

of infectious agents in certain concentrations, and with spreading factors. As a result of the increase of tissue permeability the infectious agent is dispersed over a larger area of the skin, and the infection is enhanced to a considerable degree.

On the other hand, as has been stated, very young animals often fail to react locally or they react poorly to a variety of materials injected, although the systemic reactions may be more pronounced than in adult animals. The tuberculin reaction and the Arthus phenomenon are good examples of this point, as has been shown experimentally by Freund. The same phenomena take place in adult animals when tuberculin or serum is injected intradermally in certain amounts into prepared hosts, together with relatively large amounts of spreading factor. After such an injection the dispersion of the material is so great that the concentration per unit area of tissue is insufficient to induce a local lesion, although the systemic reactions are not modified. The same is true when bacteria are inoculated along with spreading factor in certain concentrations (32).

It would seem, therefore, that the great tissue permeability of young animals, together with the low reactivity of the cells, is responsible for the phenomena described. In the newborn rabbit and mouse the organization of the dermal intracellular system is so rudimentary that cohesion in the skin is all but lacking, and it is almost impossible to inject material intradermally. No wonder then that some infections or toxic agents give in the newborn individual only minimal local lesions but kill the host with generalized lesions.

Modification of Infection by Neoplastic Viruses by the Age of the Host

Cancer is usually a disease of adult life and old age. It may be useful to apply the general principles just reviewed concerning age and infection to the problem of cancer, not only because of the importance of cancer but also because the undoubtedly infectious forms of the disease provide the best materials to show the profound changes that infection undergoes in the course of aging.

Discussion will be primarily concerned with avian cancer. The chicken is the animal species showing probably the highest incidence of cancer, and the tumors that develop are in every way comparable to those that occur in other animals and in man. It has been well known since the work of Ellerman in 1909 and of Rous and others in 1912, that leukoses and all mesenchymal tumors of chickens are caused by viruses and, for reasons which cannot here be discussed, a similar cause for epithelial tumors is suspected.

Paralleling the growth of chickens, the blood serum develops the power to act upon or neutralize many different antigens, such as red cells, bacteria, and viruses—at least those viruses inducing sarcomas and endotheliomas (33). The factors in the serum responsible for this neutralization show the properties of antibodies, but the possibility that other agents play a part in the inactivation of viruses is being investigated. Other manifestations of the resistance of old chickens are the regression of transplantable tumors and the frequent incapacity of both spontaneous and transplantable tumors to be transmitted to other hosts by filtrates or even by cells. Spontaneous tumors in very old chickens are benign in most instances (45).

The embryo and the newborn chick are practically devoid of any demonstrable defense and accordingly are extremely susceptible to neoplastic viruses, as they are to vaccinia and to many other infectious agents. However the point important for the purposes of this paper is that these vulnerable hosts do not respond to the tumor viruses by developing cancer. If a sarcoma virus is injected, the chicks develop an extremely characteristic non-neoplastic condition of a destructive type, which is called hemorrhagic disease. The most obvious manifestation of this disease is the development of "blebs" throughout

the vascular system, a result of attack by the virus upon the vascular wall. Under the influence of the blood pressure, the weakened wall gives way and may finally rupture, causing death by hemorrhage. In all probability the virus induces destructive lesions in other tissues as well, but these lesions are much harder to detect (34, 35).

The hemorrhagic disease can be indefinitely transmitted from embryo to embryo or from chick to chick, but every time that infected tissues are injected into older animals, cancer rather than hemorrhagic disease develops. The disease has been observed to be caused by the viruses of all the rapidly growing, transplantable, spontaneous chicken sarcomas, as well as by the many variants obtained in pheasants, guinea fowl, turkeys, ducks, and pigeons (36, 37).

If progressively older hosts are injected with the sarcoma viruses, it is observed that older chicks and pullets develop a combination of hemorrhagic and neoplastic lesions, while full-grown chickens develop tumors which not infrequently regress after an initial phase of growth. Exceptions are found, certainly not a surprising fact when the relativity of all manifestations of aging are considered. A counterpart of these experiments are experiments showing that after injection of chicks with tumor viruses, treatment with serum from normal adult chickens makes the chicks respond to the viruses much as do adults (38).

The following observation, still unpublished, adds more to the subject. Among the variants of the Rous sarcoma virus recently obtained in ducks there is one which has the property of inducing lesions in the central nervous system of ducklings in addition to lesions of other tissues. It is, therefore, a neurotrophic strain, the first known among cancer viruses. The interesting point is that the lesions induced are hemorrhagic (blebs) and remain so as long as lesions are induced, a phenomenon which takes place only during the first weeks of life under ordinary circumstances. As mentioned earlier in this review, some viruses are neurotrophic for only a limited length of time after birth and before constitutional barriers, developed by aging, protect the central nervous system against the viruses (16). In the duck, the central nervous system evidently becomes inaccessible to the virus before the period when this tissue would have responded to the virus by developing tumors. Another factor involved may be an innate incapacity of the nervous tissue to respond to the virus by developing tumors. Whatever the explanation, I can state that there is a tissue in an animal species which, as far as my work goes, responds to a cancer virus by developing only non-neoplastic lesions.

The same duality in the manifestations of a single virus as determined by the age of the host is also found in other types of neoplastic infection, although it is realized that these lesions are not recognized as cancer by the orthodox pathologist. Some examples will follow.

The virus of the rabbit fibroma if injected into adult rabbits, even in massive amounts, induces a mild circumscribed lesion, the fibroma, which invariably regresses, leaving the host solidly immune. However, if the same or a lesser amount of virus is injected into newborn rabbits, a diffuse, essentially inflammatory and destructive lesion follows which kills the animal in a few days. Still a third type of disease is induced when minimal amounts of virus are injected into newborn rabbits. There follows a rapidly growing tumor, inducing satellite nodules and sometimes metastases, and having features of a sarcoma. Other studies have shown that the variable resistance of the host is responsible for the phenomena observed. An expression of this resistance is the acquired neutralizing power of the blood serum for the virus, which is very high in the adult, nil in the newborn animal massively infected, and intermediate in the newborn animal infected with minimal amounts of virus (39).

Blakemore (40) has shown, and the finding has been duplicated by other authors, that highly virulent strains of lymphomatosis injected into chicks induce a purely

necrotizing disease involving the heart and liver. However, in the more resistant animals that survived, typical lymphomatous tumors developed later. The observations of Bosc in 1903 (41) and of Glover in 1928 (42) show that the proliferative lesions, which resemble adenocarcinoma, typical of sheep-pox, are those generally present in older individuals, while distinctive inflammatory lesions occur in younger individuals. In the mild forms of the disease only papillomata develop. Still another case is the development of osteopathies, in many respects similar to Paget's disease of bone, in chicks injected with some of the duck variants of the Rous sarcoma. This will be more completely analysed in the following sections.

In summary, the examples given prove that in a number of diseases caused by "neoplastic" viruses, neoplasia is only one phase in the life history of the virus, a phase which is manifested only when the host is endowed with a certain degree of resistance to the virus. In every case this resistance is associated with aging, and is expressed either by the previous existence of a natural antiviral power in the blood serum, as in the case of chicken tumors, or by the acquisition of this power under the stimulus of the specific antigen, as in the case of the rabbit fibroma.

It is safe to state that any pathologist could be challenged to even suspect a neoplastic process when examining sections of the hemorrhagic disease produced by sarcoma viruses, of the necrotizing condition caused by the lymphomatosis virus, or of the acute inflammation induced by the fibroma virus. These examples alone would justify the statement made early in this review that age may so change infection that the different phases of a single infectious process appear to be induced by entirely different agents.

Other Aspects of the Problem of Age and Infection

Studies on the adaptability of chicken tumor viruses to foreign species have disclosed facts which throw light on some phases, either little investigated or entirely unsuspected, of the general field of aging and infection. The first problem to be analysed involves the age of the recipient host as a factor in determining whether or not a virus from a given species, such as the chicken, will infect another species, for example, the duck. The second problem concerns the importance of the age of the donor host, the chicken, in determining whether a virus will or will not vary and after infecting, become adapted to another species—for example, the duck.

The basic finding in the first problem is that infection of the duck is possible only if the duckling is infected with filtrates of the chicken tumor (Rous sarcoma) during the first day after hatching. If cell suspensions instead of filtrates are injected, the period of susceptibility is somewhat longer. Two types of lesions, early and late, may develop following these injections. The early lesions, which develop a few weeks after the injection, consist of hemorrhagic blebs, as described in chicks, either exclusively, or combined with small tumors. Transplantation of these tumors into older ducks fails in every case, but transplantation into chickens induces tumors identical to the original Rous sarcoma. In other words, these early tumors in ducklings are induced by a virus which has not varied and remains a chicken virus. The late lesions, developing sometimes many months after injection, consist of tumors of different sorts in various locations, and which, on transplantation, grow in ducks of practically any age but grow poorly if at all in chickens. In this case, the tumor is induced by a virus that has varied, one that has become adapted to ducks and is no longer a chicken virus. The duck variants of the Rous sarcoma can infect chickens, provided that very young individuals are injected, with the result that early and late lesions also develop. Among the late lesions, leukoses and osteopathies analogous to Paget's disease of bone may develop (36). Essentially the same events take place

when pheasants, guinea fowls, and turkeys are injected with the Rous sarcoma virus, but the period of susceptibility after hatching varies greatly, according to factors inherent in each species (37). The number of different tumor variants that can thus be obtained is practically limitless.

In the case of ducks, the short period of one day splits the postnatal life of the individual in two tremendously unequal spans. Yet the state of susceptibility of the first span, the first twenty-four hours after hatching, may have a decisive influence on the second span of life, for tumors fatal for the host may develop many months after the injection of virus.

What goes on in the duck during the first hours of life as a result of which a total resistance against the virus is achieved is an extremely puzzling question. Earlier in this review, mention was made of several infectious agents which easily infect and kill the chicken embryo but to which the adult chicken is totally insusceptible. In some cases, indications of resistance are apparent in the later days of embryonal development, as, for instance, in the case of herpes virus, as studied by Anderson (43). Chicks are supposed to be resistant to that virus as well as to others to which the early embryo is fully susceptible. In the case of vaccinia, the embryo is susceptible and so is the newborn chick, but the susceptibility fades away quickly during the first weeks of life, simultaneously with the appearance and increase of antiviral properties in the blood serum.

Studies made over the last twelve years on the genesis of mammary gland tumors in mice by the staff of the Jackson Memorial Laboratory, notably Bittner and more recently by many others (44), have proved that there is present in many tissues of mice from cancerous strains an agent which when transmitted through the milk to the progeny causes breast cancer to develop much later in life, provided certain genetic and hormonal requirements are fulfilled. Adequate experiments have shown that the agent exerts the most pronounced effects when administered to the progeny in the earliest postnatal period, the animals rapidly developing a resistance in the process of aging. Thus here, as in the case of duck tumors, a short period of postnatal susceptibility to a virus-like agent may have the most devastating effects at maturity. The reaction of ducklings infected with the virus of the Rous sarcoma—and other tumor viruses as well—and to a lesser extent the reaction of mice to Bittner's virus are extreme examples of a process which may occur rather frequently in infection. It is known to occur to a certain extent in some forms of tuberculosis, thus motivating the phrase of von Behring that the disease of the adult is only the epilogue of a drama, the first act of which was played in the cradle.

The second problem for consideration —whether the age of the donor host determines the adaptation of a virus to another species of animal—was disclosed as the result of the following observations. When attempting to adapt the virus of the Rous sarcoma to ducks by injecting newborn animals with cell suspensions, it appeared that the age of the chicken bearing the tumor was just as important a factor as was the youth of the recipient host. Thus, tumors grown in chicks were easily transferable to ducklings and could even be carried through them in several passages but no generalization took place; tumor regression was the rule, and in consequence no adaptation to the duck was achieved. On the other hand, tumors grown in old chickens were not easily transferable to ducklings, but in the few cases where growths were obtained, adaptation to the new species followed. The tumors grown in chickens of an intermediate age seemed to be the most adaptable to ducks, although this adaptation was far from being a constant occurrence (45).

These observations have to be related to the diminishing susceptibility of aging birds to tumor viruses. The chicken tumor virus infecting progressively older birds shifts from a highly favorable to a highly

unfavorable medium. Adaptation takes place most easily between these two extremes, when presumably conditions in the medium become adverse, but do not yet so affect the virus as to suppress the tumor completely or cause the tumor to regress. Therefore, it is not that the tumor virus varies as a consequence of infecting the duck, but rather that ducks are infected by an easily adaptable virus because this virus has previously varied in the chicken.

The process is not dissimilar from what is commonly observed with bacteria grown in artificial media. In the case of the staphylococcus, for instance, the population in young cultures is perfectly uniform, the colonies derived from all individual cells being identical. Yet, if cultures a few weeks old are plated, a variety of abnormal forms are obtained, some of which breed true while some die and others revert to the original type after a few passages. After several weeks, plating gives no results because all the bacteria have died. Whether it be by mutation or selection, the variation of the bacterial strain is caused by a reaction to a medium which becomes more and more adverse as a result of aging and the competition for food. Comparable phenomena are sometimes observed in persons convalescing from infectious diseases.

The phenomenon of variation in infection with age which has been described for tumor viruses may be of importance in the general field of infection. This phenomenon means that variation of infectious agents may take place frequently in aging individuals and that the new variants may be the source of potentially more virulent strains. In the case of cancer, it indicates that the adverse conditions created by aging may cause a virus which manifests itself as non-neoplastic in the embryo or in the young, to induce a great variety of neoplastic tumors as age increases.

The Synergic Development of Age Resistance

In order to explain the major susceptibility of the young individual to infection, the following factors have been discussed: lack of antibodies normally present, inability to elaborate antibodies under the proper antigenic stimulation, lack of organization of tissues, defective phagocytic function, and high tissue permeability. It is obvious that all these factors have a part in the defense mechanism, although in a particular infection the role played by one of them may be more prominent than the roles played by others. It is also obvious that in the process of aging all these factors producing susceptibliity are modified at the same time and when one of them is changed experimentally the others are changed accordingly. The work of Lurie (46) is especially revealing in this respect. Lurie has demonstrated that in rabbits from inbred strains resistant to tuberculosis, there is a pronounced capacity to manufacture specific antibodies and develop an allergic state, to localize the infection at the portal of entry, to phagocytize the bacilli by mononuclear activity, and, indicative of a low tissue permeability, to restrict the spread of intradermally injected dyes. However, these characteristics of defense are found in low degree in individuals from an inbred strain susceptible to tuberculosis; and, as has been indicated, they are all but absent in very young individuals from any species.

It would be superfluous to try to emphasize the close interrelation between aging and endocrine effects. The work of Loeb and his collaborators (47) and of others has shown that it is possible to modify the character of the stroma of organs through the action of hormones. Continuous treatment with estrogens results in the same increase in resistance that is observed with advancing age. With estrogen treatment, some of the changes of aging have been reproduced experimentally. Now it has been shown that estrogen protects against certain experimental diseases, such as syphilis and vaccinia, and is able to cure some spontaneous human diseases such as gingival and vaginal infections. It is also

known that females are more resistant than are males to certain diseases and that this resistance can be overcome by testosterone (48). On the other hand, estrogen enhances the production of antibodies to a variety of antigens and lowers tissue permeability considerably (49; 32 for complete references).

Opposite endocrine effects can also be observed. Lurie has found that tissue permeability is higher in female than in male rabbits, and that injections of corpus luteum hormone increase this permeability in all animals. These studies were motivated by the greater susceptibility of females to tuberculosis. Other hormones that seem to modify infection in various directions are becoming known. It seems clear that the endocrine phenomena involved in aging are complex; factors of dosage and above all factors of genetic susceptibility may modify the hormonal effects in many directions (32). Apparently contradictory phenomena are also observed. Thus, estrogens, the inductors of resistance, can induce cancer under certain conditions, while androgens counteract the process to a certain extent (44).

Because there is at least a superficial analogy with the previous observation on the contradictory effects of different hormones, mention should be made of those cases in which susceptibility rather than resistance is acquired in the process of aging. For instance, it is known that infants and children are refractory or much less vulnerable to some dangerous diseases, such as yellow fever and typhus fever; newborn dogs and rabbits are resistant to the viruses of distemper and rabbit-pox, respectively; early chick embryos are unaffected by doses of diphtheria toxin which are lethal for older embryos; the renal and hepatic cells of some very young mammals are practically insusceptible to chemical poisons to which the adult's cells are extremely sensitive. The explanation may be advanced that there is a passive protection by immune bodies acquired from the mother during gestation or through nursing, but the process can also be conceived of as a lack of differentiation of the cells resulting in an absence of the proper receptors through which the cells combine with the virus or toxin.

However, it should be repeated that on the whole the best source of natural defense against infection is what may be called well balanced physiologic aging. The succession of events that lead to so-called acquired immunity can not conceivably take place, at least in an efficient way, unless the individual possesses in some degree the attributes of natural resistance which culminates in physiologic maturation or aging.

These attributes—antibody production, phagocytosis, tissue organization, and perhaps others—develop in a synergic manner, there being at present no valid reason to assume that one antedates and is the cause of the others. It may be that some day such a reason will be found, or another definite factor will be discovered as the cause.

It does not appear illogical to think that age resistance may be the result of some sort of physiologic specialization in the general process of ontogenetic development. On the other hand, age resistance may be the result of ontogenetic development as a whole without any particular proximal causes.

Additional Comments

No doubt age resistance in some cases suppresses infection completely. On the other hand, the examples given of neoplastic viruses show that unquestionably in other cases the infection is only modified by age. Thus the question arises: How frequently does this phenomenon occur? How many disease conditions of the aged are merely modified forms of known infectious processes of the young? Since the days of Pasteur and Koch it has been the acute infection, the infection of the young, that has been almost exclusively studied, and, as statistics show, it is the young who have most benefited from medical research. The systematic

study of infection of the old has not yet started.

Man came into being in a contaminated world. Although in a philosophical sense, infection is not a phenomenon inherent to life, reality shows that many of the simpler living forms have an indispensable need for the higher forms to accomplish their destiny. Consequently, infection—parasitism, commensalism, symbiosis—is to all intents and purposes a part of life itself, just as form and function are.

The comparative study of form and function has been of fundamental importance in the development of modern anatomy and physiology. Anatomists and physiologists study life from the most simple manifestations to the greatest complexities, the result of phylogenetic development. Despite what has been accomplished, it must be admitted that, so far, infection has been studied in most cases in an unsystematic manner, each worker being exclusively interested in this or that particular disease, disregarding the broad biologic laws which form the basis of each problem.

There is no reason why infection should not be studied systematically along the same pattern as anatomy and physiology. The time has perhaps come to begin the comparative study of infection with the purpose of learning about the manifestations, first in phylogenetic development and second in ontogenetic development—that is, through aging.

People are resigned to aging because everybody does age. Yet, how many manifestations of senility may be of a remote infectious origin and, therefore, theoretically avoidable? If cancer is considered as a typical episode of aging, at least some forms of the disease would fall into the avoidable category. How many other diseases of old age will time show to be avoidable? What would old age be like in a sterile world?

Summary

(1) Numerous clinical and experimental observations have conclusively demonstrated that parallel with the process of aging there develops an increased resistance to infection. This concept holds true despite exceptions, of which the most important are those concerned with the decreased vulnerability of the newborn and the nursling to several infections to which the adult is extremely vulnerable.

(2) The cause of age resistance is discussed: whether it can be ascribed to a refractory state of the cell itself, either congenital or both acquired and hereditary, such as is known to occur in unicellular organisms. It is shown that the processes of acquired immunity are subordinated to aging, and so it is pertinent to study the influence of aging, especially on virus infection. The following is found: First, there are practically no data available as to whether the cells from susceptible or immune animals do or do not combine with the virus, as has been so well studied in the case of bacteriophage confronted with susceptible or resistant bacteria; second, there is evidence, in the few cases investigated, that viruses do not multiply except in the presence of cells from susceptible animals, but that the resistance is a congenital property of the cell; third, when the whole organism acquires a resistance, either by aging or after conflict with a particular virus, the cells remain perfectly susceptible in most cases; and fourth, there are a few examples of cell resistance, gathered from unrelated fields, which are perhaps compatible with the idea that in some cases cell resistance is acquired by immune reaction, by aging, or both. The chief value of these examples is to point out a promising field of research.

(3) Data on the acquisition of age resistance by the whole organism are abundant. The known attributes of resistance are the following: (a) the presence of natural antibodies against numerous antigens; (b) the development of antibodies under the proper specific stimulus, and of an allergic state; (c) organization of the tissues, and proper phagocytosis; and (d) decreased tissue permeability.

(4) These principles of age resistance find a clear expression in the field of neoplastic infection. Several examples of this type of infection are analysed—namely, sarcoma of chickens, fibroma of rabbits, lymphomatosis of fowls, and sheep-pox. In all these cases the infection gives a clinical and histopathologic picture which differs according to the age of the host. The disease in the embryo and newborn is of an inflammatory, destructive type, whereas the disease in the adult is neoplastic. The form of the disease can be correlated with the variable resistance of the host, manifested by typical immunologic properties in the blood serum.

(5) Another aspect in the relation of age to infection is concerned with those cases where the period of susceptibility to an infectious agent lasts for only a short postnatal period. An infection taking place at this period may not manifest itself until later in adult life. The two most important examples given are the infection of ducks by chicken sarcoma viruses and that of mice by the virus present in the milk, which induces mammary gland cancer.

(6) Consideration is given to the importance of the age of the donor-host in determining whether a virus from this animal will or will not adapt itself to other species by a process of mutation or selection. The only example so far known is that of a chicken sarcoma virus which will become adapted to ducks only when it has undergone previous variation in an aging chicken —that is, when the medium becomes adverse, much as happens when bacteria are cultivated in artificial media. Therefore, a virus which induces non-neoplastic conditions in the embryo and in the young, induces not one but many types of neoplastic tumors in the aging host, through the process of variation. The possible importance of this phenomenon in originating new and more pathogenic variants of ordinary viruses is commented upon.

(7) The diverse manifestations of age resistance seem to develop in a synergic manner, and experimental modification of one manifestation entails modifications in the others. Experiments on hormonal effects and on infection of inbred strains of animals are especially interesting in this respect. The manifestations of age resistance are those which immunologists have always associated with natural or acquired immunity. The succession of events that leads to immunity could not conceivably take place unless the individual possesses in some degree the attributes of natural resistance which culminate in physiologic maturation or aging.

(8) What has been learned from neoplastic infection, and from other sources, indicates that the resistance of the old individual does not always result in a complete suppression of the infection. This resistance may but modify the infection in such a way that its manifestations are unrecognizable as compared to manifestations of the same infectious agent in the young individual. It becomes justifiable to wonder how many diseases or episodes of old age fall in this category. Since the early days of bacteriology, it has been experimental infection of the young which has been almost exclusively studied, and it is the young which have most benefited. It is time now to study systematically experimental infection of the old.

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In this review no references have been given to those general topics, often reviewed and discussed by others, in which the relation of infection to aging is remote, such as the reactions of unicellular organisms, the cultivation of filterable viruses, and the natural resistance of species. The reader can find summarized data and references to original articles in treatises such as those of Perla and Marmorston (1), Van Rooyen and Rhodes (2), and Topley and Wilson (3). Previous reviews on some aspects of the subject treated in this paper are those published by Baumgartner (4) and by Perla and Marmorston, Van Rooyen and Rhodes, and Topley and Wilson. References to phases of work directly concerned with age and infection refer, in most cases, to key articles in which an extensive literature on the subject is quoted.

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British National Health Insurance—The Workers' Pride

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THE BRITISH SYSTEM OF NATIONAL HEALTH INSURANCE, CHARACTERIZED BY GROWTH BUT LITTLE CHANGE, HAD ITS INCEPTION IN THE POLITICAL AMBITIONS OF ONE MAN. AT THE TWENTY-FIFTH ANNIVERSARY OF THE LAUNCHING OF THE BRITISH PLAN, LLOYD-GEORGE ADMITTED THAT "THE NEED OF THE LIBERALS TO TAKE VOTES FROM THE GROWING LABOR PARTY HAD MORE TO DO WITH THE ADOPTION OF HEALTH INSURANCE THAN THE NEED OF THE POOR FOR MEDICAL CARE." THAT THE PROGRAM HAS BEEN POPULAR IS SEEN IN THE FACT THAT THERE HAS BEEN CONTINUOUS PRESSURE TO FORCE THE INCLUSION OF AN EVER GREATER PART OF THE WORKING CLASS UNTIL IN 1944 ABOUT 90 PER CENT OF THE WORKERS WERE COVERED.

As was pointed out in the article on German health insurance, which appeared in the April issue of the JOURNAL OF GERONTOLOGY, the history of the first fifty-five years of the German system is one of change and development. On the other hand, the story of the first thirty years of the British system is one of growth but little change. If both could be represented pictorically, at their beginnings and again at the latest dates for which there are fairly complete data, the picture of the German system in 1938 would bear as little resemblance to that taken in 1883 as the average picture of a man in his fifties bears to a photograph taken when he was a few months old. Conversely, the facsimile of the British system of 1943 would appear to be merely an enlargement of its photograph of 1913. This is the more remarkable because, as one British Parliament member remarked, the British law was "perhaps the most unworkable statute ever passed by Parliament." Moreover, the British system was subjected to many of the same forces which molded the German system.

In the first place, the British system, like the German, had its inception in the political ambitions of a single man. The German law was passed because Bismarck wanted to defeat the Social Democrats. At the dinner which marked the twenty-fifth anniversary of the launching of the British scheme, Lloyd-George admitted that "the need of the Liberals to take votes from the growing Labor Party had more to do with the adoption of health insurance than the need of the poor for medical care." In England as in Germany, the political benefit derived by the ruling party from the enactment of the law was short-lived, for the Labor Party made health insurance a plank in their platform as soon as they realized how popular it was with the working classes.

And popular it was. The proof of this is seen in the fact that there was a continuous pressure to force the inclusion of an ever greater part of the working class. In the beginning, in 1913, less than half of the workers in England and Wales* were included; by 1944, about 90 per cent were covered. This, however, did not represent much more than a third of the total population, because since the fundamental medical benefit was not administered by the Approved Societies, which administered the cash benefits, there was no general adoption of a dependents' benefit as there was in Germany.

The expansion of the British system took form, first, of including more and more manual workers until all were covered, and secondly, of gradually raising the income limit for nonmanual workers from £160, the limit in force prior to 1919, to £420, the

* There is a separate scheme in force in Scotland, for which complete data are not available. There is, however, no reason to believe that conclusions deduced in connection with England and Wales would not be equally valid in Scotland.

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limit established by the law of 1941. The age limits also were altered. In 1911, all workers between the ages of 16 and 70 were covered; in 1944, the limits were from 14 to 65 years (60 for women). The drop at the lower limit closed the gap between medical inspection in school and medical care under the health insurance system. The reduction of the upper limit to 65 followed the inauguration of the old age contributory insurance scheme, which applies to all over 65. Its implementation in 1925 broke the last tie between the national health insurance scheme and old age protection.

In Germany, the administration of the whole health insurance setup was divided between two types of organizations, the Kassen, which were charged with supplying all kinds of benefits pertaining to the first six months of sickness, and the Institutes, which had surveillance over all matters concerning long-duration invalidity. In England, the administration of the system was likewise divided between two different types of organizations, but their responsibilities were differentiated by type of benefit rather than on a temporal basis.

The administration of all cash benefits, whether paid for sickness lasting six days or six years, was turned over to the Approved Societies. Many of these Societies had existed prior to the implementation of the health insurance system. In fact, some could trace their history back to the guilds of the fourteenth century and had been assisting disabled members for most of the intervening six hundred years. But these Friendly Societies had fallen upon evil days by the early part of the twentieth century. They were weak, having only between four and five million members, and were, moreover, in financial straits. They welcomed the chance to administer the cash benefits, not only because that would give them a certain income but because the law of 1911, which implemented the scheme, provided these Friendly Societies with a credit of £10,000,000, "which enabled them to start afresh with a slate clear of all their past financial errors."

Of course, it was necessary to set up new organizations to provide for the great influx of members. Here, another factor, not present in Germany, entered the picture—that of the British industrial insurance companies. When the plan was first proposed, these companies were fearful lest enactment result in loss of business for them. The government knew that if the insurance agents fought the bill it could never be passed, so two concessions were granted. The first was that the British scheme should not carry with it a funeral benefit. This made Britain the only country without a funeral benefit provision in its health insurance system. The second concession was that the industrial insurance companies were allowed to set up their own societies for the administration of cash benefits. The companies had to create special societies, because in order for an organization to qualify, it had to be "non-profit" and "democratically managed." After Lloyd-George acceded to the companies' demands, the insurance agents became enthusiastic boosters of the plan, and the slogan of the campaign, "Ninepence-worth for fourpence," became a household word. Sir William Beveridge thinks that the companies made a good bargain, because their societies have been effective advertising agents and from the beginning have insured more than 40 per cent of the members of the system.

These insurance societies and the Friendly Societies, taken together, formed the Approved Societies, which were charged with the administration of the cash benefits.

There is a strange parallelism between the history of the Approved Societies and that of the German Kassen. Both groups were weak or nonexistent when the insurance systems were inaugurated. In the course of time, some of the Societies and Kassen became extremely strong, others amalgamated or dropped by the wayside. In 1912, there were 2,200 Approved Societies in England, in 1941, only about 800. Despite this great decrease in number there was a wide divergence in the size and power of the Societies. Seventy had less than a hundred members; one had only thirty-four. On the other hand, twenty-four had more than fifty thousand and one had more than two and a half million.

As in Germany, the causes for this decrease in the total number of Societies were partly governmental, partly internal. Some Societies could not meet the high standards of solvency. Others resented the fact that in 1928 the Minister of Health was granted the "right to investigate the affairs of a Society," to require an amendment to the Society's rules, and to penalize it for nonconformance by a reduction of the governmental subsidy for administration. Such provisions are strangely reminiscent of the governmental supervision imposed on the Kassen four years earlier. No wonder that some of the Societies considered health insurance "too much of a nuisance to bother with."

The big internal force which strengthened the strong at the expense of the weak was competition. In one respect, the Societies were in a more advantageous position to carry on a competitive campaign than the Kassen, because in England there were no industrial or territorial restrictions. If a worker decided to join a certain Society, he was perfectly free to do so, unless his physical condition disqualified him.

However, in another respect the British Societies were in a less favorable competitive position than the Kassen, for they were more limited as to funds and as to the benefits they could offer. The British law, unlike the German law, did not give the Societies any leeway in the matter of contributions except in case of a deficit. The money for the benefits was collected, on a flat rate basis, from employers and employees and turned over to the Ministry of Health, which, in turn, paid the Societies a fixed amount for each member and a governmental subsidy for administration.

The power of the Societies to offer generous benefits was curtailed not only by lack of funds but also because authority over medical benefits was given to another group of organizations. Because of this, the Societies could not, like the German Kassen, provide medical coverage for the dependents of the insured workers. They had to content themselves with paying higher cash benefits than were required by law and furnishing "additional benefits."

The British law, like the German, set forth certain minimum benefit standards to which the Societies had to conform. The maternity benefit consisted of a lump sum (£2) for each insured parent. The wage loss benefit, instead of being a certain proportion of the wage, was a flat amount for all men workers between the ages of 21 and 65, and was a small amount—never higher than 18s.—because the British had the theory that the benefit should furnish only a "floor of protection" instead of being an indemnification for the actual wage loss. This "floor of protection" idea was feasible in Britain but would have been inapplicable in Germany, where there was a greater wage differential.

Naturally, this minimum amount was increased over the years to correspond to the increased cost of living. In fact it was almost doubled, for it was only 10s. prior to 1920 and 18s. after 1941. However, the statutory minimum was not very important. In 1941, the departmental committee on sickness benefit claims found that many of the Societies were paying between 25 and 30s. Recently a benefit in excess of 30s. has not been uncommon.

As in Germany, this relatively high benefit was paid only for a certain period from the fourth day of illness. Originally, this

minimum period was three months, but it was doubled in 1920. The minimum disability benefit was also increased. In 1911, it was 5s.; under the law of 1941 it was 10s. 6d. As in the case of the wage loss benefit, the Societies have paid more liberal disability benefits than they were compelled to pay. In 1941 it was estimated that about three fourths of the workers belonged to Societies which paid, on the average, disability benefits which were 25 per cent above the legal minimum.

In addition to these extra cash benefits, many of the funds provided extra medical benefits, such as dental or ophthalmic treatments, sanatorium or hospital care, and special medicines and appliances. During the prewar quinquennium, 1935-1939, 85 per cent of the workers were entitled to some or all of these benefits. In 1943, dental service was offered to two thirds of the members, but few availed themselves of this opportunity.

In Britain, as in Germany, there has been much malingering. In 1931, the Minister of Health reported that it was "difficult to resist the conclusion that a substantial proportion of those who are at any particular time receiving sickness and disablement benefits are persons who are not incapable of work." In 1938, a medical survey showed that 15 per cent of all those receiving benefits were malingering.

One of the main causes of malingering is overinsurance. For instance, in 1935 when the disability benefit was 41 per cent of the low wage received by young boys, the invalidity rate among workers under 21 was extremely high; again, between 1920 and 1932, the benefit received by married women approximated their net earnings when the amount they had to pay for the care of their children was deducted. It is not surprising that the claims for the married women's benefit more than doubled between 1921 and 1927.

Not only did the government ease the administrative burden of the Societies by lowering the married women's benefit in 1932, but ever since the inauguration of the system the law has provided for reduced benefits for low-wage groups such as women and all workers under 21. The following table shows the variation of legal benefits for the adult group.

	1911		*1920*		*1932*		*1941*	
	Sickness	*Disabil.*	*Sickness*	*Disabil.*	*Sickness*	*Disabil.*	*Sickness*	*Disabil.*
Men	10s.	5s.	15s.	7/6	15s.	7/6	18s.	10/6
Unmarried Women	7/6	5s.	12s.	7/6	12s.	6s.	15s.	9s.
Married Women	5s.	3s.	12s.	7/6	10s.	5s.	13s.	8s.

The government aided the Societies in another way, by providing for a reduction of the benefit after six months. Many workers who found the sickness benefit ample for their simple needs decided that the disability benefit was too small. For instance, in 1927 at least half of those who ultimately recovered after six months of illness "declared off" the benefit rolls during the first month after the benefits were reduced, and another 20 per cent "recovered" during the second month. It is not surprising that an authority on Approved Society finance should have remarked drily that it was probable that the Societies would never be able to dispense with the right to reduce the benefit.

The Societies have tried to deal with the problem of malingering. When a Society suspected malingering, it appealed to the Regional Medical Officer to referee the case, sometimes in conjunction with the doctor, sometimes in spite of him. Often the Regional Medical Officer decided in favor of the Society. During both 1923 and 1930, in about 30 per cent of the cases reviewed the workers were sent back to work; in 1928 the ratio was 60 per cent. These figures are often cited to prove increase in malingering

on the upswing of the economic cycle and a decrease on the down trend. The same thing occurred in Germany.

The Societies were in a particularly strategic position to detect malingering because they employed "health visitors," coworkers of the claimants, who had sources of information as to the validity of claims which would not be available to an officer of a corporation or a governmental official. Moreover, these health visitors were eager to prevent fraudulent claims from being honored as they knew that the more claims that were paid, the less would be their own chance of getting extra benefits. That their personalized supervision has been effective is shown by the fact that experts blame the great increase in the claim rate during the war in part at least on the difficulty of getting health visitors.

The crucial question is: Has this administrative setup been more successful than the German? In 1925 the Royal Commission found that the administration of the cash benefits by Approved Societies was inefficient and extravagant.

Efficient administration by the Societies was hampered by what the Royal Commission called "the senseless dissipation of members among many different Societies." For instance, in 1925 investigators found that in Glasgow there were ninety-eight Societies which were represented by only one member. This is one reason why the British costs of administration averaged about 15 per cent of all expenditures as compared to 6.5 per cent in Germany.

The administration of the cash benefit by the Societies was inequitable, according to the report of the Royal Commission, because of the variation in the benefits among different Societies. But the Societies still administer the cash benefit. The reason is not far to seek. One authority wrote in 1941 that "it is interesting to contrast the power, the influence, and the great wealth of the Approved Societies today with their almost hopeless position before national health insurance was introduced." The following year, the *National Insurance Gazette* explained this: "The membership of Societies is numbered in the millions, and men and women in all walks of life—from humble laborers to eminent members of the peerage, from juveniles to centenarians—are proud to be included in the ranks. It is not to be supposed that the Friendly Societies will be tossed aside in some reconstruction."

However, the Societies' personalized administration notwithstanding, the claim rate in England almost doubled during the first twenty-five years of the insurance system. Much of this increase was the result of malingering. In fact, the Minister of Health admitted as much in 1931 when he said: "The main factor in the general increase in claims has been an increase in the payment of claims to persons who are not unable to work." The Societies blamed the physicians. They maintained that "the lax doctor is largely responsible, directly or indirectly, for the fact that while . . . the health of the people has improved, the amount of certified incapacity has heavily increased."

Why, then, didn't the Societies discipline the doctors and bar the worst offenders from insurance practice as the Kassen did? The answer is simple—the physicians were not under the authority of the Societies. To understand the situation, it is necessary to go back to preinsurance days when a fierce battle raged between the Friendly Societies and the "physicians' clubs" (prepayment group clinics), in the course of which, bitter enmity was engendered between the Friendly Societies and the medical profession as a whole. Because of this old enmity, it was considered impolitic to entrust the administration of the statutory medical benefit to the Approved Societies.

Therefore, Insurance Committees, composed of employees, employers and representatives of the county and Ministry of Health, were formed to provide insured workers with "treatment of a kind which can consistently with the best interests of the patient be properly undertaken by a general practitioner of ordinary professional competence and skill" and with "drugs required to effect a cure."

At first, these Insurance Committees per-

formed a more or less passive role. Any qualified physician could become an insurance doctor merely by registering with the Insurance Committee of his district. Any worker who wanted a particular physician could sign on that physician's panel. The only function of the Insurance Committee was to see to it that the doctor got paid the capitation tax (originally 9s., later 9/9) for each worker who had chosen him.

However, this condition of laissez faire did not last long. In the interests of economy, the Insurance Committees wanted physicians to prescribe the cheapest drugs; in fact, the Ministry of Health, to which the Insurance Committees were responsible, got the druggists to make out a formulary of cheap drugs, which the Committees tried to force doctors to use. On the other hand, the workers, impelled by a desire to get their money's worth, demanded the most expensive medicines. Physicians had to steer a course between the two horns of this dilemma.

There were three reasons why a physician wanted the workers to like him. In the first place, he realized that there is a definite therapeutic value in a cordial rapport between a patient and his physician. Secondly, he wanted a large insurance panel, and the size of the panel was determined by his popularity. In the third place, most doctors got about half of their incomes from their private practices. To a large degree, the private patients were the dependents of the workers. Therefore, the popularity of a physician with the workers determined his income from private work. On the other hand, if the doctor did not comply with the demands of the Insurance Committee, he could be "struck off the panel, or, as a lesser punishment, fined to an arbitrary degree."

The doctors resented what they termed "lay interference." The use of the Ministry of Health's drug formulary allowed the Insurance Committees to "prescribe various sytems of medicine despite the fact that medical discoveries are free to all." In fact, it has frequently been stated that the autocracy of the Ministry of Health was a dangerous factor. The Lord Chief Justice himself said that the treatment of the insurance doctor by the Minister of Health was "pure despotism."

Furthermore, much friction arose between physicians and insurance authorities over the validation of claims by the physicians followed by disallowance of the claims by the health visitors. The Regional Medical Officers umpired these disputes and often decided against the physicians. Moreover, when doctors were disciplined for "extravagance" or other infringements of the rules of the Ministry of Health, the Regional Officers had to decide the penalty. Nevertheless, a surprising degree of cordiality has been maintained between the practitioners and the medical supervisors. In fact, when a proposal was made to abolish the Regional Officers, the physicians voted against it. Any irritation the doctors had experienced because of the supervision was more than counterbalanced by the benefit they derived from using the Regional Officers as consultants.

The irritation caused by lay interference plus the cordial relations which existed between the doctors and the Regional Officers caused the doctors to advocate the adoption of a law to force the Insurance Committees to consult a committee of physicians on all questions of a medical nature. The passage of this law in 1942 was a great triumph for the medical profession. It might be mentioned here that one effect of the inauguration of the national health insurance system was a growth of esprit de corps among physicians. In 1942 they constituted a definite political force, whereas in 1911 they were so impotent that Lloyd-George did not hesitate to ignore them when he drafted the original health insurance act.

If the physicians were bedevilled on one side by Insurance Committees, Societies, and deputies of the Minister of Health, urging economy, they were equally harassed by their patients, who, impelled by the insurance psychosis, demanded more and more treatment and drugs. The

requests for drugs became so large and so persistent that a former Minister of Health said that the English had become "a nation of medicine drinkers." The demands for treatment were so numerous that the average doctor had to see anywhere from thirty to sixty patients a day. One popular physician estimated that, on the average, each consultation took about four minutes, but added: "Four minutes does not mean good medicine."

As in Germany, authorities differ on the question of whether the care given British workers is as good as they would have had under a system of private practice. An investigating committee from the Michigan State Medical Society reported that "the introduction of health insurance has not exerted a deteriorating effect on the quality of medical service." On the other hand, Mr. Ernest Bevin said that "the medical service given the working classes is a tragedy of incompetence." When authorities disagree, the actions of the workers themselves offer the most conclusive evidence. Ten years ago "six hundred thousand Britishers who had been compelled to pay premiums for health insurance thought so little of panel practice that they did not even register with an Insurance Committee." However, probably the fairest evaluation of the medical service under health insurance was made by a writer in the English periodical, *Labor-Management* (April-May 1943); he says that health insurance developed with "patches of brilliance and patches of gross inefficiency."

Despite the claim of the proponents of health insurance that the health of the British worker has improved because of an increased sense of security and easier access to physicians, the situation seems to be that since the introduction of health insurance, the worker has experienced more and more sickness, as judged by the claim rate both for the wage loss benefit and for medical attention. Some of this apparent increase in sickness may result from the fact that the worker now takes more and more of his minor illnesses to his doctor, some, from a possible deterioration in the quality of medical care. Part of the increase in sickness is undoubtedly the result of insurance psychoses, the yielding to which often indicates a weakening of the moral fiber. The introduction of health insurance has, then, changed the worker's physical, and probably his moral, well-being. How has it affected him financially?

From all outward appearances, he is better off under health insurance than he was under private practice. Despite the increase in the per capita cost from 18s. in 1912 to £2 2s. in 1927 (the cost dropped to £1 8s. in 1942), the male employee's contribution increased only from 4d. in 1911 to 5½d. in 1941. The governmental subsidy actually decreased proportionately during that period (from 2/9 to 1/7). On the other hand, the employer's tax almost doubled (3d. in 1911, 5½d. in 1941). But—and here is the crux of the matter—five actuarial evaluations have shown an increasing proportion of workers in Societies with deficits, although never since the inauguration of the system (except during the triennium, 1926-1929) has the benefit received by the average worker equalled the contribution paid by him.

Notwithstanding this, the workers like health insurance. By and large they agree with the dictum of the Royal Commission that the system "has, on the whole, been successful in operation." This does not mean that there has been no criticism. Far from it. The system has been criticized by Parliament, the physicians, the workers, the Societies, and a Royal Commission, but its projected reorganization will involve an expansion rather than a curtailment of its powers.

There have been three chief criticisms from various sources. One concerns the uneconomic administration of the wage loss benefit, which has already been discussed. A second criticism is directed at the meagerness of the benefits. The Royal Commission (1925) wanted the cash benefit increased to match the unemployment benefit, and another commission (the Commis-

sion for Political and Economic Planning, known as the P. E. P.) recommended the inauguration of a dependents' benefit. It is probable, however, that the 1941 increase in rates will largely obviate such criticisms. Similarly, both physicians and Societies have criticized the statutory medical benefits because specialists' services and care for dependents were not included. It must be admitted that there was reluctance on the part of some doctors to recommend the inclusion of the dependents' benefits because such a step would eliminate lucrative private practice to a large degree. However, in 1943, the Council of the British Medical Association stated that they were "prepared to extend the National Health Insurance Act to embrace practically the whole population." A third severe criticism has been of lay interference with medical procedure, particularly the administration by the Insurance Committees.

At present, new and sweeping changes as to the medical side of health insurance seem imminent. If the recommendations of the white paper of February, 1944 are put into effect by the Labor Government—and it seems probable that they will be—not only will the entire population of England be furnished with both specialist and general practitioner care, but lay interference with practicing physicians will be eliminated.

The present situation in England is very much like that in the United States in the sense that there are two types of hospitals, voluntary (here called "private") and public. Practically all specialists in England have attached themselves to one of the voluntary hospitals, where they minister to the poor free of charge. The specialists' income and the support of the hospitals are derived from payments by the wealthier patients. However, most of the hospital care for the poor is furnished by public, tax-supported hospitals, which are under the direction of local governmental authorities. Before the war, there was little interchange between the voluntary and the public hospitals, but "under war conditions, arrangements have been made for interchange of patients; specialized centers have developed." Under the new plan, the war development will be perpetuated, by having the local authorities take over the administration of the voluntary hospitals and their adjunctive specialists.

Similarly, home nursing, which is at present almost entirely in the hands of the voluntary district nursing association, will be administered by the local authorities. In other words, each area is to have self-sufficient specialist, hospital and nursing service.

Although local authorities are to be responsible for the services which are to be newly introduced into the health insurance system, the general practitioner service is to be administered on a national scale. In general, physicians are to be organized around health centers by the Central Medical Board, which is responsible to the Ministry of Health. Apparently, the powers of this board will be very similar to those of the German K. V. D. (Krankenkassenaerztliche Vereinigung Deutschlands, the semi-political professional society which the Nazis made German physicians join). The board will be able to admit a doctor to insurance practice, or bar him from it. Debarment will be tantamount to professional ruin as all the population is to be included in the system. The board will have the power to assign doctors to a center and to contract with it for the remuneration to be paid the center as a whole. Doctors not connected with a center will be paid on a capitation basis. Under such a system, the position of the British doctors will be much like that of the German doctors under the Nazis.

It is estimated that such a system will cost about two and a half times the present outlay for medical expenses, and that one fifth of the cost will be defrayed by the health insurance system. Of course, such estimates include adequate remuneration for physicians, and everyone seems pleased. However, it must be realized that the government, represented by the Central Medical Board, is the sole bargaining agent. Is it

beyond the realm of possibility that in times of depression the government may enforce economies on the system at the expense of the doctors, just as the Germans did?

In short, the criticisms of the medical situation, made by the Societies as early as 1925, are about to be answered by an entire reorganization of British medical economy, along the lines pursued in Germany just prior to the war. An important subject for conjecture is whether the fate of the Societies will be like that of the Kassen, and whether they will be taken over by the government, lock, stock, and barrel, to become a powerful bureaucracy through which the British people may be regimented. A question peculiarly important to the world is: What ideologies will this system of medicine inculcate? Only time will tell.

Summary

The British health insurance system was founded in 1913, and by 1944 it covered about 90 per cent of the workers. The administration of the system is divided, according to type of benefit, between two different types of organizations. Approved Societies administer all cash benefits. In order to appease the already existing British industrial insurance companies, the health insurance act included no funeral benefit and allowed these companies to set up their own societies for the administration of cash benefits. The wage loss benefit, instead of being a certain proportion of the wage, is a flat amount. The medical benefits are administered by different groups, known as Insurance Committees. The workers appear better off financially and they like the system, but probably the quality of care has deteriorated. The three chief criticisms have been: (1) uneconomic administration of the wage loss benefit, (2) omission of specialists' services and of care for dependents, and (3) lay interference with medical procedure. British medical economy is about to be reorganized, in answer to these criticisms, along the lines pursued in Germany just prior to the war.*

* Since this article was submitted for publication, the proposed changes have become law and go into effect Jan. 1, 1948.

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CURRENT COMMENT

Social Medicine in Old Age

In England, as in the United States, the number of elderly people is higher than it has ever been and is still increasing. According to the Beveridge report, more than 20 per cent of the English population will be over 60 years of age by 1971. Trevor Howell, writing in the *British Medical Journal* for March 16, 1946, urges prompt action on the "social and medical problems which may result from this increase of old people."

During the war, older people found well-paying jobs in domestic service and industry, but with demobilization these older workers are being replaced. Lack of occupation speeds up the aging process, in addition to creating financial problems for many.

Another problem frequently encountered concerns those old people who have no one to look after them but who do not wish institutional care nor need continuous medical supervision.

Dr. Howell advocates several ways of meeting the problems of old age. First, there should be some sort of help available to those old people who live alone so that entry into institutions can be delayed for as long as possible. Trained personnel, who have access to doctors, hospitals, and sources of domestic help, might visit the elderly unemployed at regular intervals, to see that they are well, to stimulate their interest in various hobbies and pursuits, and to assist in many ways.

When entry into an institution finally becomes necessary, the institution should be uncrowded, good medical facilities should be available, and persons who need only general care should be separated from those who need complete attention. Individual rather than mass attention to the patients should be stressed. "Some degree of privacy and personal rights" must exist, except for those actually on hospital wards.

The naming of institutions for the aged is important, in order to avoid the stigma attached to poorhouses and workhouses. But "the personal attitude of the staff in these homes and infirmaries is the most important factor in making them happy and successful."

Montefiore Home

The Montefiore Home for the Aged has during the past five years developed a program which includes occupational and recreational activities, individual handling of patients through case work, selective intake, psychiatric service, psychological testing, and student training for research purposes.

The occupational therapy department was begun in March of 1941 with the par-

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The hieroglyphics, "The Beginning of the Book for Transforming an Old Man into a Youth," at the top of this editorial page, are from the Edwin Smith Surgical Papyrus, translated by Professor John Breasted, University of Chicago Press.

ticipation of two people as contrasted with 1945 when 61 per cent of the total residency worked in one or another of the projects. During its existence, the shop has purchased an electric carpenter saw, drill press, electric sander, mimeograph, and show cases. Many of the people who now earn money in the shops had never received allowances from children or other members of their families. The shops have proved themselves a valuable source of material for study. It was learned that occupation must have realistic meaning to the aged person as well as to any other working individual. The reimbursement might be in the form of usefulness to his children or in the continuance of his earning possibilities. Because of this, the workshops are set up on a realistic money-earning basis, limited as to type of work and time in accordance with the aged person's physical capacity.

Previously, older persons were not expected to take part in recreational activities, a fact which only increased the feeling of uselessness and decline. Many forms of recreation and social life have been formed and carried on at the Montefiore Home, including games, discussion groups, dramatics, social dancing, and group singing. There has even been a move away from the importation of professional artists and toward activities carried out by the residents themselves.

One important phase has been the establishment of a case work department which has proved invaluable in helping the individual adjust to institutional life. One of its main advantages is the aid it gives in this adjustment of the resident who is often embittered at having to give up home and family life. The case worker can give the potential resident, when he enters the home, intimate knowledge of the institution's facilities, advantages, disadvantages, comforts, and limitations. She serves as someone familiar at the time of entrance, presenting the link between the old and new environment.

Another new process used here is the boarding-out plan. The home in 1945 had seven residents in boarding out places. The selection of clients for this type of residence is extremely important and should be made at the point of intake. It is a great benefit, however, to the client who, on account of his background and personality, would hardly adjust to institutional living.

Analysis of the figures for application and admittance reveal the marked change in the type of aged persons seeking admission to an old folks' home. Twenty-three admissions for the year 1945 show 3 well and 1 feeble, 14 chronically ill and 1 blind, and 4 psychoneurotics, 3 of whom had previously been in state institutions. All these findings point to the necessary revision and expansion of programs for the aged.

The home has to a great extent offered psychiatric and psychological service to the residents. This service is valuable in determining the type of work a resident can do and his reaction to institutional placement.

In the care of the aged the future will most likely bring changes and modifications in all phases of present work. New ideas in the care of the aged and especially the chronically ill will be experimented with as the interest in the field of geriatrics continues to grow.

Cooperative Living

Realizing that frustration is not inevitable, nor is old age a disease, the Cooperative Residence Club, Inc. of New York City has as its aim the attempt to give older people their full share of participation in their community. The residents of the club are not only advanced in years, but are newcomers to this country, refugees. Many of them are haunted by sad experiences in their home countries, were uprooted late in life, and often have difficulty in adjusting to a new language, customs, and way of life. It is often hard for them to find a feeling of security. Most of them come from urban,

middle class central European background and have had little experience of a voluntary character in group living.

Many who have done little in the way of housework and in caring for themselves have learned to help with the work of the club and keep their own rooms in order. Two of the residents, a former physician and a former businessman, who had never thought of entering the kitchen in their own homes, now almost daily peel potatoes. Each person is assigned tasks suitable to his ability and, as far as possible, preference. In addition, residents share together recreational and educational programs, including English classes, book clubs, and concerts and recitals by professional artists.

Each resident, upon entrance, is required to buy ten shares in the cooperative at $10 each. A substantial reserve is set aside for the original purpose of meeting emergencies and the rest is available as a working capital for general purposes and the development of the club.

Several outside workers give their time and talents to aid the club. Artists, physicians, lawyers, real estate men, accountants, and teachers have contributed much valuable consultation and professional help.

At the end of the fiscal year 1945, the club had 41 residents, including 4 couples, 32 single women, and 1 single man. Two were over 90, 6 between 80 and 90, 19 between 70 and 80, and 14 between 60 and 70. Fourteen of the residents were gainfully employed during the year, while others worked as volunteers with local social agencies.

The club has an ever increasing waiting list, but there is room for a turnover of only approximately 10 each year. There is a great need for additional units such as this one, as the delay in admittance of many of the applicants is bringing increased hardships for them. (Annual Report of the Cooperative Residence Club, Inc. for 1944-1945)

Medical Memorial Fund

More than half a million people in the United States die each year from diseases of the heart and arteries, but only 17 cents per death is spent on research in this field. In contrast, investigation on infectious diseases received $6 per death in 1940.

As the world is adjusting to the postwar era, now is the time to expand research programs in the important field of the degenerative diseases of increasing age. In addition, basic study of the processes of aging must be undertaken if a clear understanding of the cause and nature of disease is to be acquired.

In 1940, the foundations granted $4,700,000 for medical research. At least ten times that amount is needed yearly if the most prevalent diseases are to receive proper attention.

To meet this situation a new foundation —Medical Memorial Fund, Inc.—has been created. Medical Memorial Fund receives its income largely from memorial gifts. These are contributions to medical research made at the time of the death of friends or relatives. As the fund receives each memorial gift, it sends a dignified memorial certificate to the member of the family of the deceased specified by the person making the gift. The donor receives an acknowledgment card which serves as a receipt for tax purposes.

This plan appeals to many people as an appropriate expression of sympathy—a lasting memorial of benefit to mankind. Here is an opportunity for each individual to make a contribution. A fund collected as one hundred gifts of $10 is as valuable as $1,000 from one person.

The chairman of the board of trustees of the Medical Memorial Fund is Harlow Shapley of Harvard University, and the president is Henry S. Simms of Columbia University. Sound administration of the funds is guaranteed by a distinguished board of trustees and scientific committee.

Honorary members of the Lay Council include Chauncey Belknap, John W. Davis,

Marshall Field, Herbert Hoover, and Albert N. Williams.

Members of the board of trustees are A. J. Carlson, Russell L. Cecil, John V. Duncan, Guy Emerson, Harry Goldblatt, Theodore G. Klumpp, Albert D. Lasker, Chauncey D. Leake, William Loeb, Currier McEwen, William de B. MacNider, Donald G. Price, Harlow Shapley, Henry S. Simms, J. Murray Steele, Lowell Thomas, Marvin R. Thompson, D. D. van Slyke, A. Ashley Weech, George H. Whipple, and Mark Woods.

The scientific committee is composed of J. Murray Steele, A. J. Carlson, Russell L. Cecil, Harry Goldblatt, Chauncey D. Leake, Theodore G. Klumpp, William de B. MacNider, Marvin R. Thompson, Henry S. Simms, D. D. van Slyke, A. Ashley Weech, and George H. Whipple.

Individuals who wish to make their small contribution to the future will welcome the establishment of this unique foundation for medical research. The offices are located at 630 West 168th Street, New York 32, New York.

Longevity

In spite of the fact that living conditions today seem to imply a high standard of public health, a view of the entire globe reveals many diverse conditions. Louis I. Dublin and Alfred J. Lotka point out in their article on "Trends in Longevity" (The Diplomate, *18:* 61–71, 1946) that all peoples have not shared equally in the advancement of science and the technical arts. Some have been held back by adverse climatic conditions, others by outmoded traditions or sheer superstitions, and still others have lagged in following the lead of the most progressive nations.

According to Dublin and Lotka, figures for the average length of life among the various countries of the world vary greatly. Look at Sweden with an average of 63.2 years for the period 1931–1935 as compared with a bare 30 years for India and China. Between these are the figures for Germany, 59.9 in 1932–1934, France, 54.3 in 1928–1933; and Italy, 53.8 in 1930–1932. It might be noted that these figures show a downward tendency as the observer moves geographically from the northwest corner of Europe to the south and east. Note that the figure for Russia, 41.9 in 1926–1927, equals that reached by Sweden before the middle of the last century.

The change in the length of life throughout the world comes with definitely recognizable causes. Dublin and Lotka attribute it to a general rise in the standards of living, including better housing, food, education, advances in medicine and public health, control of infectious diseases, and improved working conditions.

Much has been done to improve housing conditions, but the problem is far from complete. European nations have very definite problems arising from the extensive war damage, and application of modern methods as to town planning should give opportunity for furthering general health conditions. Another great benefit derived from our modern mode of living is the provision of more abundant, better, and more diversified food. Along with this, better means of transportation have made more variety in food available to many more nations of the world.

"Another major factor, especially in more recent times, has been the increasing development of social agencies to promote health and welfare, especially our social security program. Along with this we now have far better working conditions, such as shorter hours and the introduction of industrial hygiene and safety practices which have led to more leisure hours and improved recreational facilities."

As Dublin and Lotka point out, medicine has made great advances in controlling infectious diseases, such as yellow fever, smallpox, diphtheria, scarlet fever, and whooping cough, and there has been a great reduction in the number of deaths from tuberculosis and pneumonia. Also in the field of medicine, there has been great im-

provement in prenatal and child care and a growing interest in geriatrics. Hopes for a greater increase in the length of life arise from the increasingly concentrated study of the diseases of old age.

The United States is facing a declining birth rate, disregarding the temporary spurt in the early war years, so that we are promised at best an approximately stationary population from about 1980 onward. At the same time, the past downward trend in the birth rate has caused a steady upward movement in the average age of the population, a movement which will inevitably continue for many years to come.

Social Security

The Ways and Means Committee of the House of Representatives, in studying the present social security program, was told by Secretary of Commerce Henry A. Wallace that the plan should be extended to include about 20 million farmers and businessmen not now included.

"Universal coverage is the only democratic way," Wallace said. "There is no more justification for the exclusion of some sections of our population from the advantages of social security than there would be for their exclusion from the advantages of public education."

According to Wallace, experience with the plan during the last ten years has demonstrated the feasibility of extending coverage to small businessmen, other self-employed persons, farmers, farm laborers, domestic employees, and other groups not previously included because of administrative difficulties.

Respect with Age

The fact that a person has passed his sixtieth birthday does not necessarily entitle him to great honor and respect, says Elsie Robinson in an article in the St. Louis *Post-Dispatch*. Old people should be honored providing they earn honor, but the mere fact that they are becoming old does not endow them with superior character. "A person of 60 who pampers his own laziness, malice, and conceit may be quite as obnoxious and unworthy of honor as a hoodlum of 16."

The author points out that in spite of years of experience, the elderly person deserves no special consideration unless that experience has proved valuable and he has made use of it. Some have a far richer life at 35 than others at 70. "It is not the number of years but what has been done with them that is important."

Unfortunately, too many older people are sold on the ancient tradition that long life gives them special privileges. Why should their advice be valued when they have done nothing to make it valuable? Actually, harm is done by giving praise and respect where none is due. Regardless of age, a person deserves no honor unless he has won it by personal effort, says Miss Robinson. There is no reason why normal older persons should not keep abreast of the times and command respect on their own merit.

Life to Years

Many middle-aged and elderly people fear old age in spite of the fact that there isn't much they can do about it. As Thurman B. Rice points out in his article "Adding Life to Our Years" in *Hygeia* for May, 1946, one must either die or grow old. Death is as necessary as birth, for if the average length of life were one thousand years, a birth would be a rare event and society would be largely made up of old people. Because old age is inevitable, perhaps there should be greater concentration toward adding life to years rather than years to life.

"There is no limit to such a process, for it is a matter of attaining a satisfactory

philosophy of life so that one may enjoy and utilize to the last minute the good life that he has," says Mr. Rice. "It is not the length of life that counts, but the quality, the usefulness of it."

Many of the most important lives have come to an end at an early age. Such people as Mozart, Keats, Shelley, Schubert, and Spinoza died in their thirties, and thousands of young men in their teens and twenties have recently given their lives in World War II. A well integrated old man was asked if he resented growing old. "Resent it?" he asked. "Why, if I hadn't been born when I was, I couldn't have had the parents I had. I couldn't have known my wife or my children. I couldn't have had my many, many friends and have lived in the most interesting period in history. Being born when I was, I am happy to have grown old because otherwise, I would have died long ago." And so Mr. Rice recommends that one enjoy life while he can. It is better to enjoy a short vacation—or life—than to endure a long one. Why let the good things of life turn bitter simply because they must come to an end? Why try so hard for rejuvenation when the later years can bring an equal amount of happiness and pleasure if only permitted to do so? Everyone is trying to find the life that will give the maximum amount of lasting pleasure and comfort, and lives were made to be spent wisely and well. Old age can be equally as happy as youth or middle age if only given a chance.

Homes for the Aged

Contrary to the beliefs and hopes of many, the passage of the Federal Social Security Act and old age assistance have not done away with the need for homes and facilities for caring for the aged, the blind, and dependent children. "The past ten years of administrating the social security programs has shown the appalling extent of chronic disease and chronic invalidism and the dearth of facilities for care, both public and private," says Raymond M. Hilliard in an article in *Public Welfare* for December 1945. The act itself and most of the state assistance laws contain clauses prohibiting the resident of public institutions from receiving old age and blind assistance, but, unfortunately, these are the only institutions in many states which have adequate and superior facilities for caring for old people suffering from chronic disease and invalidism. Yet, under the existing laws, people can avail themselves of this care only at the surrender of their assistance grants.

For the past two years, Illinois has realized the prevalence of chronic disease and invalidism among older people and has received many requests from voluntary hospitals that all such cases be transferred to the county homes. Faced with the need for providing nursing care to a growing number of public assistance recipients, the Illinois Public Aid Commission worked out with the county governments on an individual case basis arrangements for placing recipients of old age assistance in need of long-time nursing care in the county home. However, because of the provisions of the law, the grant had to be terminated and responsibility for meeting costs of care was transferred to the overseer of the poor. As Mr. Hilliard points out, this caused the county homes to be regarded more and more as nursing institutions rather than boarding houses for the able-bodied poor. Therefore, the county governments began to modernize and equip these homes for the care of the chronically ill. The Illinois Public Aid Commission and the county governments joined forces in endorsing amendments which would enable the counties to convert their county homes into desirable facilities for such care.

In March of 1945 there were seventy-two county homes in Illinois with a total bed capacity of 7,264. These homes are fairly well distributed throughout the state and in many instances represent the only existing facilities for care of the chronically ill. However, these homes are viewed as but

one of several units in community-wide plans for the care of the sick. Facilities of these county homes will be geared in with private nursing homes and hospitals. "The type of facility used by the particular patient will be determined by the nature of his illness and the type and amount of medical and nursing care he may need. . . . Safeguards will be established to make sure that public aid recipients and persons with borderline income have the same opportunity to receive the type of care they need as persons with more ample means." The Illinois Old Age Pension and Blind Assistance Acts provide that a resident of a county home shall be eligible for either of these two forms of assistance.

Since inmates of public institutions are not eligible for old age assistance, the expense of this project is being borne by state funds. According to Mr. Hilliard, this program seems to be filling a great need although it has been in existence for only three months. It has also stimulated county governments to develop plans for modern conversion of their homes, and has brought about recognition of the needs of the ill as a community problem demanding full cooperation in order that proper care may be readily accessible to all.

ORGANIZATION section

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Registry of Gerontology

In 1922 the Surgeon General of the Army consented to have the Army Medical Museum serve as a central repository for the American Registry of Pathology. Since that time over fifteen registries have been established. The newest is the Registry of Gerontology.

The basic idea of the registry is to have some one place where all people interested in a given field may deposit objective research material. The specimens and slides in the registry are available to all competent investigators. Hence, a comprehensive study of a subject is facilitated.

The Registry of Gerontology is sponsored by the Gerontological Society, Inc. and is at present supported by a grant from the Josiah Macy, Jr. Foundation. The committee on the registry includes: Jean Oliver, chairman; E. V. Cowdry, Walter W. Jetter, Carl Hartman, Robert A. Moore, and, ex officio, Col. J. Earle Ash and Roy G. Hoskins.

Investigators and members of the professions are urged to send objective material as it relates to aging to the registry. A pathologic report by the registrar will be rendered. All communications should be addressed to: Registry of Gerontology, Army Institute of Pathology, 7th and Independence S.W., Washington 25, D. C.

Conference on Aging in Wistar Rats
The Wistar Institute of Anatomy and Biology, Philadelphia, Pennsylvania, June 7 and 8, 1946

PROGRAM

EDMOND J. FARRIS, *Conference Chairman*

FRIDAY, JUNE 7
10:00 A.M.–1:00 P.M.
EARL T. ENGLE, *presiding*

Introductory Remarks by Edmond J Farris of The Wistar Institute

It is gratifying to be able to welcome this group to The Wistar Institute, to discuss findings of a program in which we have all been engaged for the past five years. It seems only a short while ago that the first letters which started the study were sent out, but I am sure that many of us feel as though we have aged as much as the rats, in the short equivalent time, in our efforts to prepare material for this conference, and

particularly when faced with the urgent war problems in which many here participated.

It is truly remarkable that this cooperative study now approaches a successful termination. There are twenty-two individuals represented on the conference program, and there are eleven others who were unable to participate for various reasons. These eleven have, however, promised to have manuscripts ready for publication within a reasonable time. Seven other investigators found it necessary to select substitutes during the study. One of the group, Dr. George S. de Renyi, died a year ago.

To the best of my knowledge, this is the first time that such a group has voluntarily assumed and maintained to the finish a cooperative venture of this nature.

Another phase of this program, undertaken by the Institute staff, consists of a study of the effects of emotional stimuli on the life processes of the rat. The study considers the physiologic changes, such as production of hypertension, breeding results, and anatomic modifications, such as organ weight and tissue changes, from birth to old age, as affected by emotional stimuli. The limited time available today will prevent discussion along these lines.

A word regarding the method of securing and distributing the material. Besides the animal colony and attendants, the services of at least seven workers at the Institute were required before the collaborators received any organs. Three dissectors worked against time, and we can all appreciate the difficulties in the dissecting of such small organs as the thyroid and pineal. This same team made the first and last dissections together, from birth to old age of the rats. Another team weighed the organs and fixed the tissues. Secretaries prepared records. A responsible individual handled the shipping of the material. During the entire study, only two jars were broken in the shipping, and this breakage, I think, occurred at the Christmas season.

At this time I wish to express my deep appreciation to the loyal staff who participated in the study. Dr. Eleanor Yeakel, my able associate, handled many of the details, including dissection. Miss Margaret Seitner did the weighing and fixing of organs. Miss Ruth Meeser dissected many a small organ. Mrs. Martha Tosh aided in dissecting, and in phases of the blood work, as did Mrs. Bertha Copeland. Dr. Paul Aptekman handled the details of shipping the specimens. Mrs. Lillian Cressman supervised the care of the animals in the colony, and Miss Beatrice Roberts and Miss Margaret Johnston saw that the collaborators received correspondence and records in accurate and efficient manner. Many others took part in the program in various capacities.

Words can hardly express my appreciation to Mr. Samuel S. Fels for his encouragement, when this program was called to his attention. He told me once that if I wished to apply to the Fels Fund for aid, he believed that he had some influence with the members of the Fund Board. So to Mr. Fels, and Mr. Frederick Gruenberg, the cooperative and genial Secretary of the Fund, and to the other members of the Board, we are deeply grateful for aid in making this study and conference possible.

The consensus is that each worker should publish in any journal of his or her own selection. It is requested that 75 reprints be ordered for the Institute, so that bound volumes of the reprints can be sent to each worker when the study is over.

We urgently request a set of slides from each worker for a library of slides that will be available at the Institute for any scientist desiring complete microscopic material on practically any structure in the rat, at all ages.

Finally, I wish to express my thanks to the collaborators and others for participating in this conference. I realize that many of you have sacrificed much to be able to be present. We hope you will find your stay here pleasant and profitable.

Growth of body and parts in Wistar albino and gray Norway rats, with special refference to changes in old age.

Edmond J. Farris and Eleanor H. Yeakel
The Wistar Institute, Philadelphia, Pa.

The occurrence of enlarged hypophyses in old rats.

William H. F. Addison
The University of Pennsylvania, Philadelphia, Pa.

The blood picture of rats from weaning to old age.

Edmond J. Farris.
The Wistar Institute, Philadelphia, Pa.

Changes in the spleen of the albino rat from birth to senescence.

Margaret M. Seitner
The Wistar Institute, Philadelphia, Pa.

Age changes in the vascular architecture and cell content in the spleens of 100 Wistar Institute rats, with some comparisons to human material.

Warren Andrew
Southwestern Medical Foundation, Dallas, Texas

Some histological changes in the thymus of the rat during age involution.

Christianna Smith
Mount Holyoke College, South Hadley, Mass.

Age changes in the deep cervical lymph nodes of Wistar Institute rats.

Warren Andrew
Southwestern Medical Foundation, Dallas, Tex.

2:00 P.M.–5:00 P.M.

WILLIAM H. F. ADDISON, *presiding*

Cytological studies on the anterior pituitary in various age groups of Wistar rats.

Aura E. Severinghaus
Columbia University, New York, N. Y.

Age changes in the gonads of rats.

Earl T. Engle
Columbia University, New York, N. Y.

Mammary glands of the rat during growth and senescence.

Virgene Warbritton and Ralph P. Reece
Agricultural Experiment Station, New Brunswick, N. J.

Changes with age in the adrenal glands of Wistar albino and gray Norway rats.

Eleanor H. Yeakel
The Wistar Institute, Philadelphia, Pa.

Senile changes in the ducts and alveoli of the pancreas.

Warren Andrew
Southwestern Medical Foundation, Dallas, Texas

Age changes in the rat's exorbital lacrimal gland.

Roland Walker and Vivian T. Walker
Rensselaer Polytechnic Institute, Troy, N. Y.

Spontaneous tumors.

Homer D. Kesten
Columbia University, New York, N. Y.

The size of somatic chromosomes at different ages in the rat.

John J. Biesele
Carnegie Institute of Washington, Long Island, N. Y.

DINNER—6:30 P.M.
North Garden
Bellevue-Stratford

DR. WILLIAM STEVENS—Nuclear Fission
MR. ISO BRISELLI, violinist

SATURDAY, JUNE 8
9:15 A.M.–1:00 P.M.

CHRISTIANNA SMITH, *presiding*

Senile changes in the brains of Wistar Institute rats.

Hartwig Kuhlenbeck
Woman's Medical College, Philadelphia, Pa.

Regeneration of the corneal epithelium in aged rats.

George K. Smelser and V. Ozanics
Columbia University, New York, N. Y.

Effects of age upon certain physical and chemical properties of the calcified structures of the body.

J. Edward Gilda
University of Rochester, Rochester, N. Y.

Oral and dental changes in the incisors and molars with progressive age.

Isaac Schour and J. Weinmann
University of Illinois, Chicago, Ill.

Age changes in cartilage of the larynx of rats and man (demonstrated by the Spalteholz method).

Gustav Noback
New York, New York

Changes in the temperomandibular joint with age.

Paul E. Boyle
University of Pennsylvania, Philadelphia, Pa.

Closing Remarks by Edmond J. Farris of The Wistar Institute.

As we considered the problems of aging in the Wistar rat here today, one could not help but recall the early pioneers in the history of The Wistar Institute, who more or less suggested the use of the rat as a standard tool for research. I think of Dr. Milton Greenman, the former Director, who had quite an uphill battle trying to sell the idea of raising rats for research. We confront similar problems today, in trying to establish the idea of raising monkeys, dogs, or even horses for laboratory purposes in the comparative studies of aging.

I think of the late Dr. Henry Donaldson, starting out as a neurologist and needing animals for his studies. I think of Dr. King, who has probably done more research than anyone else on the inbreeding of rats, and who made the pure inbred rat available to Dr. Donaldson for some of the records which have been used for comparison today.

I believe the findings discussed as a result of this program on aging will set an example for future coordinated studies of a similar nature, by other groups. There is no doubt but that the results will stand the test of time. Investigators of the future will undoubtedly use these fundamental findings as stepping stones to greater discoveries.

I believe this meeting has emphasized the fact that to understand the processes of aging, it is essential that the body be considered as a whole, and to do this it is necessary that the individual findings be coordinated and correlated.

We have started out separately in our own specialties, studying individual maturations and senescences. The results should be brought together. Many of the collaborators attending the conference commented on the desirability of collecting, for each rat studied, all the information available on the organs of that animal. It would be wise, therefore, if the collaborators made a card file for each animal studied. The cards should be sent to The Wistar Institute, so that condensed data sheets can be prepared for distribution to the collaborators, for consideration.

Many of you have already submitted abstracts of the present findings, for the records here. It has been suggested that we should all submit abstracts for duplicating purposes. When this material is available, we shall see that copies are sent to each of the workers.

I want to repeat, for the benefit of those who were absent yesterday, that it has been decided that the collaborators may publish wherever they think best, and 75 reprints are requested for deposit at the Institute, so that separate volumes of reprints may be bound for distribution to the collaborators.

We have requested a set of slides for the Institute's collection of slides, to form a depository that will be made available to

you, so that you can come here and receive a sample of each tissue at any age. The slides should be submitted only after you are ready to publish. Take full advantage of your own material, and do not worry about the Institute collection for the present. When you have secured from your slides all the desired information, then it will be time to make them available to others.

In addition to the normal control animals, the organs of which were supplied to the collaborators, we have, at the Institute, performed some 500 complete autopsies on emotionally stimulated animals of both the gray and albino strains. These animals had been stimulated from weaning to old age. Our purpose in completing these was to initiate an investigation in psychosomatic medicine, and it is hoped that we shall learn more about the changes in animals that have been exposed daily to upsetting stimuli.

It would be impossible for the Institute workers to prepare the organs from all these experimental animals, for a study. From the normal material supplied to you, you have dealt with the structure of your special interest. We can now offer you these same structures from the experimental series, if you feel that the material would be of value. We realize this tissue work is not simple, yet here is an opportunity to determine whether emotional conditions and upsets throughout the life span effect any changes in the organs. Arrangements for the conduct of this phase of the program will be sent out later.

Yesterday I said that I hoped you would have an enjoyable and profitable meeting, and I did not know at the time how the meeting was to come out. I do feel that we have had a successful meeting. Many questions have been raised, and many answers have been found. The questions which Dr. Schour asked, about diet and metabolism, the questions regarding the endocrine system, and many others, suggest more work for many. The findings cannot be interpreted at the moment, but I believe that as your final papers are submitted for publication, the problems of aging will somehow mushroom like the atomic bomb, with success in the particular purpose for which the problem was undertaken.

Finally, I wish to thank each and every one of the participants for attending the meeting, and for contributing so much to the discussions. I know you have sacrificed a great deal to be here. Many of you could attend only one day. You have come from long distances, from heavy schedules, and we do appreciate it.

I wish to express my thanks to the presiding officers, Dr. Christianna Smith, Dr. W. H. F. Addison, and Dr. Earl T. Engle.

We shall stand adjourned until another Conference on Aging is necessary.

DR. CHRISTIANNA SMITH: I would like to express for the collaborators—I am sure I am speaking for the rest of them—the appreciation of everything that has been done by The Wistar Institute for us, and for the chance to have been able to see, as we have these last two days, the studies on organs other than the ones we have been interested in and to see the future of working in cooperation.

It seems to me one of the difficulties has always been that when we have been working on one organ and wanted very much to know what was happening in the other organs, we really could not get the answers to the questions we wanted answered. Therefore this cooperative project is one of great promise.

I want to thank you and your colleagues for the hospitality which you have extended to us for these two days.

LEGAL ASPECTS

The following are extracts from the Bulletin on State Legislation, Health, and Welfare of the Social Security Board Errors may occur in both bill numbers and titles.

ARIZONA

Old-age Assistance, Amount—S. 8XX. Increases the maximum amount of assistance to be paid to old-age beneficiaries from $40 to $50 for any calendar month. Introduced April 24 and referred to Appropriations Committee.

H. 8XX. Relates to amount of assistance old-age assistance statute; increases from $40 to $50 maximum assistance to any recipient. Introduced April 23 and referred to Judiciary, Appropriations, County and County Affairs, and Ways and Means Committee.

H. 9XX. Relates to amount of assistance under old-age assistance statute; increases from $40 to $50 maximum assistance to any recipient. Introduced April 23 and referred to Judiciary, Appropriations, Efficient Government, County and County Affairs, and Ways and Means Committees.

Old-age Assistance, Eligibility—H. 6XX. Relates to eligibility for assistance to needy aged; amends Section 70-202, Arizona Code 1939, by deleting subparagraph 9 thereof which reads: "9. Has not during the twelve months immediately preceding his application received an income from all sources not including contributions and assistance from public or private charities of a net value exceeding $360.00 per annum." Introduced April 23 and referred to Judiciary, Appropriations, Efficient Government, County and County Affairs, and Ways and Means Committee.

CALIFORNIA

Aged, Needy—A. 420. Amends Section 2140 of the Welfare and Institutions Code, relating to aid to the aged; and prohibits discrimination against practitioners of particular types of healing arts in the rules for the administration thereof. Approved June 9, 1945. Chapter no. 801.

Aged, Care of—S. 32X. Amends Section 2302 of the Welfare and Institutions Code, relating to the inspection services licensing agencies for the care of the aged, making an appropriation therefor, and declaring the urgency thereof, to take effect immediately. Introduced January 10 and referred to Social Welfare Committee. Amended February 1 in Senate; passed Senate February 5. Reported favorably in Assembly February 8. Passed in House February 14. Chapter no. 107.

GEORGIA

Old-age Pension—S. 240. Provides that old-age pensioners shall receive $30 per month in the future. Introduced January 14 and referred to Public Welfare Committhe.

KENTUCKY

Old-age Assistance—H. 10. provides that old-age assistance not be denied or reduced for indigent parents because of liability of adult children. Introduced January 8 and referred to Ways and Means Committee in House January 16. Reported favorably in House January 31. Recommitted to Ways and Means Committee February 6. Passed House February 14.

H. 385. Prohibits the reduction of old-age assistance and aid to the needy blind by reason of any casual or incidental income or resource thereafter becoming available to recipient. Introduced February 19 and referred to Juvenile Courts and Children's Homes Committee February 25. Vetoed March 26.

Old-age Assistance, County Administrator—H. 409. Gives county judge the power to act as county administrator of old-age assistance. Introduced February 20 and referred to Ways and Means Committee. Reported favorably in House March 1.

Old-age Assistance—H. 22. Provides that old-age assistance shall not be denied indigent parents because of liability of adult children. Introduced January 9 and referred to Ways and Means Committee. Reported unfavorably in House March 4.

MASSACHUSETTS

Aid to Aged and Children—S. 575. Authorizes the Department of Public Welfare to enter into reciprocal agreements with certain other states relative to the granting of aid to dependent children and to the aged; authorizes the temporary granting of aid to dependent children and of old-age assistance to persons who have made permanent changes of residence to certain other states. Approved June 25, 1945. Chapter no. 458.

Old-age Assistance—H. 1354. Memorializes Congress for payment by the Federal government of one-half the expense of old-age assistance up to $50 per month for each person receiving benefits thereunder. Adopted April 4.

H. 2151. Further regulates the granting of old-age assistance, so called. Approved July 23, 1945. Chapter no. 683.

Old-age Assistance Fund—H. 2097. Provides that expenditures from the old-age assistance fund shall not be made without appropriation. Approved July 23, 1945. Chapter no. 684.

Aged, Minimum Payments—H.1169. Establishes minimum amounts to be paid under the old-age assistance law. Introduced January 17 and referred to Pensions and Old-age Assistance Committee. Reported unfavorably in Senate March 21.

Old-age Administration—H. 783. Provides for administering of the old-age assistance law by pension bureaus. Introduced January 17 and referred to Pensions Committee. Withdrawn in Senate February 14 and in House February 11.

Old-age Assistance—S. 215. A Resolution memorializing Congress to amend the federal laws relative to matching by the federal government of amounts expended by states and their political subdivisions on account of old-age assistance. Introduced January 14 and referred to Constitutional Law Committee. Passed Senate April 10 and House April 16.

Old-Age Assistance, Appeals—H. 780. Relates to appeals under the old-age assistance law. Withdrawn in House March 19.

Old-age Assistance, Budgets—S. 160. Increases the food and clothing budget in the old-age assistance law. Introduced January 10 and referred March 19 to next annual session.

Old-age Assistance, Eligibility—S. 256. Reduces eligibility under the old-age assistance law to 60 years. Introduced January 14 and referred to Pensions Committee. Withdrawn in both Houses March 14.

S. 328. Makes certain persons 60 years of age or over eligible for old-age assistance. Introduced January 14 and referred to Pensions Committee. Withdrawn in both Houses March 14.

H. 593. Provides for granting old-age assistance to needy persons upon reaching the age of 60. Introduced January 14 and withdrawn in both Houses March 14.

H. 784. Makes certain persons 60 years of age or over eligible for old-age assistance. Introduced January 17 and withdrawn in both Houses March 14.

H. 785. Makes needy persons eligible for old-age assistance upon reaching the age of 60. Introduced January 17 and referred to Pensions Committee. Withdrawn in both Houses March 14.

H. 992. Reduces from 65 to 60 years the eligibility age of applicants for old-age assistance. Introduced January 17 and withdrawn March 18.

H. 993. Provides that the age requirements of applicants for old-age assistance be reduced and increases the amounts of such assistance. Introduced January 17 and referred to Revision and Old-age Assistance Committees. Withdrawn in Senate March 18.

H. 994. Reduces from 65 to 60 years the eligibility age of applicants for old-age assistance. Introduced January 17 and withdrawn in Senate March 18.

H. 995. Recommends that the minimum age requirements for recipients of old-age assistance be reduced to 60 years. Introduced January 17 and withdrawn in Senate March 18.

H. 1171. Provides that persons 60 years of age be made eligible for benefits paid under the old-age assistance law. Introduced January 17 and withdrawn in both Houses March 21.

Old-age Assistance, Medical Care—S. 259. Relates to the furnishing of medical care to recipients of old-age assistance. Introduced January 14 and referred to Pensions Committee.

H. 782. Relates to payment of certain expenses for medical and other services rendered to persons eligible for old-age assistance. Introduced January 17 and referred to Pensions Committee.

H. 794. Provides for furnishing recipients of old-age assistance adequate hospital services. Introduced January 17 and referred March 19 to next annual session.

H. 1180. Relates to the furnishing of medical care to recipients of old-age assistance. Introduced January 17 and referred March 19 to next annual session.

Old-age Assistance Law—H. 991. Provides for legislation to make certain changes in the old-age assistance law. Introduced January 17 and withdrawn in both Houses March 14.

Aged and Infirm, Housing—H. 130. Resolve providing for an investigation by the Joint Committee on Public Welfare relative to the matter of housing aged and infirm persons who are placed in the care of the Commonwealth. Introduced January 2 and referred to next annual session.

Aged Persons, Pension Bureaus—H. 1388. Amends the old-age assistance law with respect to eligibility age and amounts of assistance; provides for the administering of said law by pension bureaus. Introduced January 17 and referred to Pensions and Old-age Assistance Committee. Reported unfavorably in House February 7. Withdrawn February 19.

Eligibility, Old-age Assistance—S. 116. Further regulating eligibility to receive old-age assistance. Introduced January 7 and referred to Pensions Committee. Reported unfavorably in House February 7. Withdrawn February 19.

Old-age Assistance—H. 167. Makes certain persons eligible for old-age assistance, notwithstanding earning of wages by their children. Introduced January 2 and referred to next annual session in House.

H. 166. Relates to the granting of old-age assistance. Introduced January 2 and referred to Pensions Committee. Referred to next annual session.

Old-age Assistance, Aliens—S. 42. Authorizes the granting of old-age assistance to certain deserving aliens. Introduced January 2 and referred to Pensions Committee.

H. 229. Extends benefits of the old-age assistance law to parents of children who have died while serving in the armed forces of the United States in time of war, notwithstanding that such parents are not citizens. Introduced January 3 and referred to Pensions Committee.

Old-age Assistance, Eligibility—S. 41. Reduces the age at which persons shall be eligible to receive old-age assistance to 60 years. Introduced January 2 and withdrawn in House March 7.

H. 290. Makes needy persons eligible for old-age assistance, upon reaching the age of 60. Introduced January 7 and withdrawn in both Houses March 14.

H. 291. Reduces the age requirements of applicants for old-age assistance. Introduced January 7 and withdrawn in both Houses March 14.

S. 40. Further regulates grants to recipients of old-age assistance. Introduced January 2 and referred to Pensions Com-

mittee. Amended in House by substitution of H. 1169, March 19.

H. 394. Equalizes the minimum monthly payments under the old-age assistance law. Introduced January 9 and referred to Pensions Committee. Reported favorably in House March 26. Recommitted to Ways and Means Committee in House March 26.

Old-age Assistance, Insurance Policies—H. 395. Clarifies the provisions relative to insurance policies held by an applicant for old-age assistance. Introduced January 9. Reported by substitute, H. 1643, in House Mar[illegible] 26.

H. [illegible]43. Relates to insurance policies held by an applicant for old-age assistance. Introduced March 26 and referred to Ways and Means Committee.

MISSISSIPPI

Old-age Assistance, Eligibility—S. 12. Amends Section 7221 of Article 3, Mississippi Code of 1942, Volume 5, so as to change the requirements of eligibility for assistance to the needy aged, by adding two subsections (f) and (g); declares relatives not contributing to the care and support of the needy aged not to be treated as resources. Also, that non-income homesteads, used and owned by the applicants, shall not be treated as resources. Introduced January 9 and reported unfavorably in Senate January 29.

Old-age Assistance—S. 288. Amends Section 7225, Mississippi Code of 1942, to omit the requirement that assistance to a needy and aged person would not be given if he or she is being maintained by any county, municipal, state, national or private institution at the time of receiving assistance. Introduced March 1 and referred to Finance Committee.

H. 843. Amends Section 7271, Mississippi Code of 1942, so as to make needy aged persons eligible for old-age assistance when inmates of certain institutions. Introduced March 11 and referred to Pensions and Social Welfare Committee.

Old-age Pensions, Severance Tax—H. 696. Provides for a new gas and oil severance tax; provides for allocation of said tax to counties and old-age pension fund. Introduced February 28 and reported unfavorably in House March 19.

Old People—H. Res. 25. Condemns activities of certain individuals in their attempt to mislead the old people of the state of Mississippi. Introduced March 29 and adopted March 29.

MISSOURI

Old-age Assistance, Eligibility—S. 23. Establishes the 1944 valuation as a basis for evaluating the dwelling houses of needy persons as it applies to the determination of eligibility for old-age assistance. Introduced January 30, 1945 and amended in House March 27, 1946. Passed with emergency clause in House March 27. Senate refused to concur in amendments March 29. Bill went to conference.

NEW JERSEY

Old-age Assistance, Pari-Mutuel Tax—A. 210. Provides that pari-mutuel race track "breakage" shall be paid to the State for reimbursing county welfare boards for old-age assistance. Introduced February 11 and referred to Judiciary Committee.

NEW YORK

Old-age Assistance—A. 1319. Provides that a person eligible for old-age assistance shall receive $50 a month. Introduced February 7 and referred to Social Welfare Committee.

A. 2078. Provides that old-age assistance shall be given to any person who has not cash bank deposit or life insurance policy with cash surrender value in excess of $500; other restrictions appear also. Introduced February 26 and referred to Social Welfare Committee.

RHODE ISLAND

Old-age Pensions—H. 1015. A Joint Resolution urging Congress to give greater federal aid to states for old-age pensions and for

aid to dependent children. Introduced April 11 and passed House April 11. Passed Senate April 12.

SOUTH CAROLINA

Old-age Assistance—H. 986. Amends law relating to old-age assistance, so as to further provide for the payment of benefits to persons of 70 years of age and older having no support of own. Introduced February 14 and referred to Ways and Means Committee.

S. 784. Increases amounts to needy persons under act providing for old-age assistance. Introduced February 12 and referred to Social Security Committee. Passed in Senate March 27.

Old-age Assistance, Residence—H. 1000. Prescribes the necessary length of residence in this State for a person receiving old-age assistance. Introduced February 19 and referred to Social Security Committee. Passed in Senate March 20. Approved March 25. Governor's act no. 703.

VIRGINIA

Old-age Assistance, Eligibility—S. 70. Amends the "Virginia Public Welfare and Assistance Act of 1938," relating to the eligibility of aged persons, dependent children, and blind persons for aid and assistance under the act. Introduced January 24 and referred to Committee on Public Institutions and Education. Reported favorably in Senate February 6.

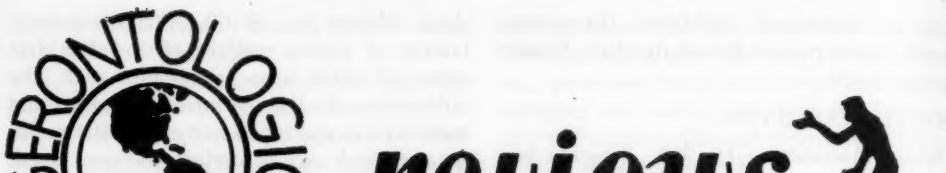
Aged, Homes for—S. 69. Authorizes local boards of public welfare of counties and cities to enter into agreement with the authorities of other counties and cities and with certain approved homes, for the maintenance and care of certain indigent aged, infirm, chronically ill, or incapacitated persons. Introduced January 24 and referred to Committee on Public Institutions and Education. Approved February 28. Chapter no. 68.

S. 72. Authorizes the State Board of Public Welfare to fix standards and make regulations for the operation of certain homes for aged, infirm, chronically ill, or incapacitated persons; requires compliance with such standards. Introduced January 24. Approved March 2.

WYOMING

Old-age Assistance—S.J.R. 1X. Proposes a constitutional amendment that "any home, hospital, or other institution established by the State for the care of the aged or infirm persons" shall not be under the control of the State Board of Charities and Reform. Introduced April 16 and referred to Judiciary Committee. Passed both Houses April 22. Approved April 25.

H. 2X. Provides for the establishment of "The Wyoming Home for the Aged." Introduced April 16 and referred to Judiciary Committee. Passed both Houses April 22. Vetoed April 24.



EQUIPMENT AIDS FOR THE AGING PERSON

During World War I occupational therapy was stimulated to develop equipment and techniques that made useful activities practical for those confined to bed, according to Louis J. Haas (Occupational Therapy and Rehabilitation, *25:* 1–4, 1946). This development is especially needed for those who must make a satisfactory adjustment and must function normally with one hand, in order for such one-handed persons to overcome a fear of being different or handicapped. Patients with but one hand are found in all age groups—combat casualties, industrial and other accident patients, and persons suffering some of the disorders accompanying the aging process. Although the aged person is more conditioned to slight interruptions in normal functions than is the younger person, it is more difficult for him to take the initiative in overcoming physical handicaps.

The first step in psychologic readjustment is to stimulate interest in a traditionally two-handed craft. The patient is allowed to practice and develop his skill until he realizes he is accomplishing wonders with only one hand. This indirect attack is important in developing self confidence and in overcoming the patient's basic fear of being different. Once he realizes he can perform a certain operation with one hand as well as others can with two, his psychologic handicap disappears, and he responds well from then on to constructive suggestions. It is therefore important to develop or modify equipment and techniques for the performance of various crafts so as to permit more and more one-handed persons to achieve success in these crafts. Such activities as book binding, mechanical and architectural drawing, art metal work, wood rasp carving, decorative and under-glaze painting, chair caning, clay modeling, free-hand drawing, typing, and water color and oil painting have been so developed and modified. They are described in *Equipment Aids for Those Having One Hand* by Louis J. Haas.

Among the first of the equipment aids developed was a sewing frame which could be used to bind books by persons with only one hand. The perfection of this aid led to the development of others, so that ultimately books could be bound by one-handed persons as well as by two-handed persons. Next, a clamp to hold objects was devised so wood rasp carving could be done. This clamp could be adapted for whittling, carving, or chipping. Bed stands, portable tables, and book holders were some of the other aids developed to make available for the one-handed person many hobbies for which two hands are usually considered essential. These aids enable the handicapped or aged person to work with confidence, which in turn speeds readjustment. Such equipment is adaptable, flexible, and simple, to allow for expansion so that many other hobbies can be utilized to sustain interest for any age group for indefinite periods of time.

JOSEPH H. HILSMAN

CHANGES IN BRAIN WITH AGE

That there are inconstant gross and microscopic changes in the structure of the nervous system with advancing age, varying greatly from person to person, is stated by Moore in his *Textbook of Pathology* (W. B. Saunders, Philadelphia, 1944). Atrophy of the convolutions, widening of the sulci, loss of ganglion cells, gliosis, and slight internal hydrocephalus have been observed. In many instances the loss of nervous tissue has a direct relation to the presence and intensity of arteriosclerosis of the cerebral arteries, but this cannot be taken as a generalization. All of the changes are usually conspicuous in patients who have clinical senile dementia.

There are two types of presenile atrophy of the brain that present a similar clinical picture with sharply different pathologic alterations. Both begin in late middle life and consist of a subacute mental involution with certain localizing signs such as agnosia, apraxia, and aphasia. These two pathologic alterations are Pick's lobular atrophy and Alzheimer's disease.

In the former, the lobes of the brain are atrophic, especially the frontal and temporal lobes. Other parts are less commonly affected. The average weight of the brain is 1,000 gm. Microscopically, there is a loss of ganglion cells in the first and second layers of the atrophic gyri. There are loss of Nissl substance and collection of the neurofibrillae at the periphery of the cell. Within the involved area there are hyperplasia of astrocytes and increase in the number of microglia.

Alzheimer's disease is characterized by a brain that is diffusely atrophic, with slight thickening of the leptomeninges. Two histologic changes are constant: the formation of senile plaques and disturbances in the neurofibrillae. The plaques vary in size and consist of an acellular mass of argyrophilic substance surrounded by distorted microglia cells and swollen, tortuous nerve fibers. The changes in the neurofibrillae are thickening, fragmentation, and final disintegration of the axons. In the ganglion cells a similar change, together with collections of neurofibrillae at the periphery of the cell, is observed.

Rothschild (American Journal of Psychiatry, *93:* 757–788, 1937) briefly surveyed the literature and studied the pathologic changes in 24 cases of senile psychoses. He found no parallelism between the severity of the parenchymatous changes of the brain and the age of the patients. There was a lack of correlation between the histologic changes and the degree of intellectual impairment.

Recently, Riese (Journal of Neuropathology and Experimental Neurology, *5:* 160–164, 1946) studied the brain of 18 patients, aged 77 to 107 years, in an attempt to correlate the pathologic changes with the length of the clinical course. Thirteen of the patients suffered from senile dementia of from eleven months' to fourteen years' duration. The diagnosis in 4 case was "psychosis with cerebral arteriosclerosis." One patient was a 90 year old woman with a diagnosis of "involutional melancholia," for which she had been institutionalized for thirty-five years. In some instances the exact onset of the disease could not be determined; in others, a more or less sudden deterioration took place after a slow initial course.

The anatomic features considered in Riese's study were: convolutional atrophy, cytoarchitecture, changes of the individual cells, and satellitosis (chosen as a criterion of glial activity). Three cortical areas were studied: area 4 of Brodman (FA of Economo), area 17 (OC) and area 24 (LA).

Riese found that an overwhelming majority of the brains of extremely old persons showed at least some degree of cortical atrophy, diffuse or regional in distribution. The degree of cortical atrophy was not necessarily proportionate to the age of the patient. The cytoarchitecture was surprisingly well preserved even in the brains of the extremely old. Although cell changes

were consistently present, these changes were not proportionate to the age of the patient. Neither the degree of cortical atrophy nor the extent of cell destruction was proportionate to the duration of the clinical history. There was no constant vulnerability of the three cell types studied (pyramidal, granule, and spindle). Satellitosis was not a constant feature, and there was no parallelism between the degree of cell destruction and satellitosis. The latter showed a definite predilection for the anterior part of the brain. All of the anatomic changes described occurred regardless of the type of clinical picture.

It may be concluded, therefore, that in the light of present knowledge, the inconsistencies in any attempt to correlate the anatomic changes in the brain of the aged with the clinical observations must be attributed to differences in the capacities of individuals to compensate for cerebral damage.

FRANK M. TOWNSEND

AGE CHANGES IN THE PLACENTA

The occurrence and significance of lipoids, glycogen, calcium, iron, alkaline phosphatase, and basophilia in the human placenta have been reported on by Wislocki and Dempsey (Endocrinology, *35:* 409–429, 1944; American Journal of Anatomy, *76:* 277–301 and *77:* 365–393, 1945). A more recent report (Endocrinology, *38:* 90–109, 1946) adds acid phosphatase to this list.

Calcium is found in a formed state (soluble in acids) in the subepithelial portion of the stroma of the villus in early pregnancy. It diminishes in amount as gestation advances.

Iron is similar to calcium in location and behavior but has a somewhat patchy distribution in the stroma.

Glycogen is found almost exclusively in the cytotrophoblasts of the epithelial islands and columns. Occasionally it is seen in small amounts in the cytoplasm of the syncytium.

Lipoids exhibit the properties of steroids and are found throughout pregnancy in both syncytium and cytotrophoblasts.

Both syncytium and cytotrophoblasts show a pronounced basophilia of the cytoplasm in early pregnancy, which decreases as gestation advances. This basophilia has been shown to be destroyed by incubation with ribonuclease. The nuclei of the syncytium become smaller during the latter half of pregnancy. During the last month this deep-staining property tends to decrease and some nuclei appear faded or unstained.

In the middle span of pregnancy, alkaline phosphatase appears in the subepithelial portion of the stroma in small amounts. As the basophilia disappears, an increasing amount of alkaline phosphatase appears in the cytoplasm of the syncytium, becoming abundant at term. None occurs in the nuclei.

In the middle span of pregnancy, acid phosphatase, like alkaline phosphatase, is seen in small amounts in the subepithelial stroma, disappearing later. Near term, as the intense basophilia decreases in the syncytial nuclei, acid phosphatase accumulates in considerable amounts in the nuclei and perinuclear zone. None is seen in the cytotrophoblasts nor in the decidua.

Wislocki and Dempsey interpret some of these changes in terms of function in an interesting manner. The basophilia of the syncytial cytoplasm, related to the presence of a ribonucleoprotein, is, according to their reports, associated with production of chorionic gonadotrophic hormone. The lipoids in the syncytial cytoplasm are related to the steroid hormones produced by the placenta. The subepithelial deposits of calcium and iron in early pregnancy are physiologic depots which disappear as vascularization of the villus progresses. Glycogen storage is related to avascularity, ischemia, or anoxemia. The inverse relation

between alkaline phosphatase and ribonucleoprotein of the syncytial cytoplasm corresponds to the changes in Nissl substance and phosphatases in neurones described by Bodian and Mellors (Journal of Experimental Medicine, *81:* 469–488, 1945) during retrograde degeneration of nerve fibers. In contrast to this, both nucleoproteins and alkaline phosphatase are abundant in osteoblasts, a fact interpreted by Wislocki and Dempsey (Physiological Reviews, *26:* 1–27, 1946) to suggest that the phosphatase is secreted by these cells.

A study of two specimens of hydatidiform mole revealed that the viable portions containined no calcium or iron, showed prominent basophilia of the syncytial cytoplasm and abundant steroid deposits, and possessed great amounts of glycogen both in stromal and epithelial cells. In terms of function, those activities which concerned placental transmission appeared to be definitely impaired (absence of calcium and iron in the villi), whereas those that were concerned with synthesis and secretion (basophilia and lipoids) were variably retained. Finally, there was accumulation of glycogen as evidence of abnormal and inadequate circulation.

Two specimens of placenta, one from a patient with severe preeclampsia at four and one half months and another with eclampsia at the same stage of gestation, were examined. Histologically, many of the terminal villi were like those in pregnancy at term, and histochemically there was a marked increase in both alkaline and acid phosphatase in the syncytium. Calcium was present in the syncytium and diffusely in the stroma. Glycogen was found in the stroma of a number of large and medium-sized villi.

Wislocki and Dempsey suggest, on the basis of the premature aging and the excess of phosphatases which they found, that there may be a disturbance of nucleoprotein metabolism in the toxemias of pregnancy. The abnormalities of calcium and glycogen distribution are attributed to some impairment of blood supply of the villi. It is interesting that in a placenta at term from a patient with nephritis and renal hypertension, no abnormalities of histologic structure, cytoplasmic basophilia, or phosphatase reactions could be demonstrated.

R. E. JOHNSON

INFLUENCE OF AGING ON POWER AND ENDURANCE

An important gerontologic problem concerns the limits of the physical work which can be expected from persons of advancing years. There are two ways of conducting an inquiry into the effects of age—namely, the statistical study of different age groups, and the study of individuals as they progress from decade to decade. The latter method has been the basis of several experiments performed by Percy M. Dawson of the department of physiology at Duke University.

Observations on a single subject from the fifth to the eighth decade (Dawson and Hellebrandt, American Journal of Physiology, *143:* 420, 1945) indicated that while the working capacity decreased steadily, being about 50 per cent at 71 years of what it had been at 41 years, the circulatory reaction during maximal performance was much the same at each age. It was also shown that the maximum reduction of the resting pulse rate as a result of vigorous training for exercise was the same at 41 and at 71 years.

In a recent communication, Dawson (Research Quarterly, *16:* 95, 1945) again reports detailed experiments on a single subject. The data consist of four sets of observations: (1) on cycle-ergometer rides;

(2) on long-continued mountain climbing (endurance); (3) on short, brisk mountain ascents (speed); and (4) on road walking. A complete medical and athletic history of the subject is given. It is interesting to note that he was not exceptionally endowed physically but had participated in hiking and mountain climbing since boyhood. This type of exercise is closely allied to that forming the basis of observations in this report. The highest record on the cycle-ergometer was at 41 years (1830 kg. m. per minute); at 57, the rate was 60 per cent of this, and at 71, 50 per cent. The highest record for long mountain climbs indicating endurance was made at 33 years; at 23, endurance was 68 per cent of this, and at 68 years, 35 per cent. The maximum ascending speed in mountain climbing occurred at 31 years of age; the speed at 68 years was 82 per cent, and that at 71 years, about 71 per cent, of the rate at 31. The longest walking distance was at 50 years (45 miles); that at 21 years was 87 per cent of this. Preceding all of these experiments, the subject underwent rigorous training programs, preparation for the cycle-ergometer being 3 mile runs on thirteen occasions. Dawson states that the observations with the cycle-ergometer are the most accurate and the most carefully studied.

These data support the contention reported before (Hellebrandt and Dawson, Proceedings of the Federation of American Scientists for Experimental Biology, *1:* 39, 1942) that maximum strength and endurance are reached at about 30 and the ability to carry on sustained work dwindles during the latter years of mature life. However, the 71 year old subject in Dawson's report demonstrated surprisingly little decline in endurance and ability to do hard muscular work.

Obviously, a major factor in considering the problem of aging on power and endurance is the rate of recovery from exercise at various ages. Dawson and Hellebrandt (American Journal of Physiology, *143:* 426, 1945) report that the number of days necessary for complete recovery from exercise is appreciably greater at 68 and 71 years than at 57 years. The difference in days needed for recovery from exercise between early adulthood and late adulthood would be even greater. Dawson and Hellebrandt also report that the margin of safety (defined as that margin between maximum effort and collapse, actual or impending) narrows appreciably as age increases.

No general conclusions can be drawn from this experimental work for several reasons: (1) observations based on the individual study of many subjects must be done before accurate curves can be drawn; (2) power and endurance must be measured in a value based on tests applicable to everyday usage; and (3) greater range in age and frequent intervals of testing must be included. However, the field of age physiology is of recent origin and importance. The facts presented should prove suggestive to other workers.

DAVID OLIVER

BOOKS

PREVENTIVE GERIATRICS

A FUTURE OF PREVENTIVE MEDICINE, Edward J. Stieglitz, The Commonwealth Fund, New York, New York, 1945. $1.00.

This small volume of seventy-three pages is one in a series of monographs sponsored by the Committee on Medicine and the Changing Order of the New York Academy of Medicine, and published by the Commonwealth Fund.

The author, a practicing geriatrician in Washington, D. C., and consultant in gerontology, United States Public Health Service, hastens (in the preface) to call attention to the selection of the indefinite article in the title, pointing out that " . . . there are other possible futures and one or more of such might well prove more desirable than that herein presented."

The meat of the book is contained in three chapters designated: "Definitions," "Health Over the Last Forty Years," and "A Program for Preventive Medicine."

If there is one theme throughout the whole book it is: "Medical science has outgrown the older definition that health is that state of being which exists in the absence of disease. . . . There are various degrees of health. Health is relative. Health can be no more absolute than such states as freedom, slavery, wealth, poverty, beauty, or ugliness." This concept has been accepted for children, and concerted efforts have been made to improve the health of "well" babies. Stieglitz believes: "It is absurd that such medical guidance should be applied only to infants and children. Adults are also entitled to an opportunity to improve their state of health."

It is argued that a shift in emphasis from defense (preventive medicine) to attack (constructive medicine) will help to overcome the sense of negativeness and inertia so common in mankind. The public must be educated to the immense advantages of a higher level of health. The idea that health is an inalienable right must give way to one that health is a privilege and that privileges invariably entail equivalent responsibilities.

At the same time that there is reorientation from prevention of disease to maintenance of maximum attainable health, Stieglitz urges increasing attention to the degenerative diseases and failure of health in older persons. This is not to be accomplished by simple transfer of pediatric practice to geriatric practice, because "an older person is almost never wholly 'normal' and certainly never ideally in the fullest possible health. The scars of having lived are inevitable. The borderline between disease and the normal depreciations of aging is hazy and wide." Hence, the health inventory, not just a periodic health examination, is an integral part of Stieglitz's future of preventive medicine.

In summary, *A Future for Preventive Medicine* includes (1) continued use of both the wholesale and retail methods to prevent disease by control of environment and by increasing individual resistance, and (2) exploitation of possibilities in the improvement and maintenance of health, especially in the later years of life.

Stieglitz concludes: "The future of preventive medicine is bright, whatever its precise course may be. But fruitful accomplishments will take time and effort. Research, education, and great extension of the application of personal health construction can go far—just how far will depend

chiefly upon the intelligence, energy, and integrated motivations of mankind. Medical science can *give* health to no one, but it is daily becoming more competent in guiding those who wish to *earn* health. Prevention of disease is not enough; even good health can be bettered. Approach to the optimum should bring to life not only greater length but greater depth and breadth as well. Then men will live long enough, deep enough, and wide enough to think. That might even mean lasting peace. This goal is worth any effort."

ROBERT A. MOORE

THE ME'S IN MY SOCIAL COMPLEX

THE WAY OF AN INVESTIGATOR, Walter B. Cannon, W. W. Norton and Company, Inc., New York, New York, 1945. $3.00.

Although Dr. Cannon states in the preface that "admittedly this is a book about one of the me's in my social complex—in the main about me as a scientific worker," a glance at the table of contents reveals much more than science. And reading brings to mind many of the deeper attitudes and viewpoints of one of America's greatest scientists and humanists—for thirty-seven years George Higginson professor of physiology at the Harvard Medical School.

Fate was acting under a guiding hand when in 1870 Colbert Hanchett Cannon, a railroad worker, and Sarah Wilma Denio, a young school teacher, were brought together in Prairie du Chien, the site of Fort Crawford, where William Beaumont made his classic observations on digestion, in 1820. A century later their son, Walter Bradford Cannon, was destined to add immeasurably to our knowledge of the digestive tract.

There are few problems of the young investigator, or the professor, or the administrative head of a department, which are not covered. For example, in the chapter on "Passing on the Torch" there are discussions of the advantages of using productive scholars for administrative services in American universities. The young physician wavering between a career of research and of practice may well read and reread the chapter on "Fitness for the Enterprise." The traits important for a life of investigation are listed as "curiosity, imaginative insight, critical judgment, thorough honesty, a retentive memory, patience, good health, generosity, and a humble attitude." The words of encouragement from the philosopher to the young man are: "A beginner who seriously plans a life of productive scholarship, should not be disheartened if he thinks his qualifications do not meet requirements. Training and practice may not lead to perfection, but they will surely compensate for early inadequacies."

The young investigator who is worried about the problem of outside demands on his or her time will get sound advice in the chapter on "Being a Citizen." Although admitting the advantages of uninterrupted time for research, Cannon states: "Nevertheless, the scientist is also a citizen and may feel a compulsion to engage in services which he as a citizen has opportunities to perform." The personal acceptance of this dictum is exemplified in Walter Cannon's long defense of medical research, his vigorous support of the Spanish Republic, his participation in aid to China before general realization of the threat to peace from the Japanese, and his acceptance of the presidency of the American-Soviet Medical Society. Would that more scientists might heed the words: "The unchecked pursuit of [the] most cherished desires [of the scientist] depends immediately on the liberty which a democratic government most reliably provides. He does well, therefore, to watch over it and, if necessary, to go forth

from his 'serene attachment to the processes of inquiry and understanding' to battle for its security."

Walter Cannon was deeply interested in gerontology; he was a charter member of the Club for Research on Ageing. In the last chapter, entitled "The Fruitful Years," he gives a bird's-eye view of his thoughts about the period of life in which there is greatest scientific productiveness, the discrepancy between physiologic old age and chronologic old age, and adjustment for retirement.

In a few words, pages 219 and 220, there is a complete thumbnail sketch of the "bodily changes" as "the decades slip by" —the pigment spots on the skin, the long hairs in the nose and ears, the shaggy eyebrows, the creaky joints, limitation of the effectiveness of the homeostatic devices, rigidity of expansion of the chest, stiffening of the arteries, and change in the near point of clear vision leading to what Holmes termed the "trombone age."

A guide for research in gerontology may be gained from: "The physiological limitations of old age arise because our bodies are composed of a group of cooperative organs. All goes well as long as each one performs adequately its role in the complex. It is when an important organ becomes impaired and fails to 'play the game' that a break occurs." In this quotation, the word "physiologic" may well be replaced by "social" and "organs" by "activities," for a basic statement on the sociologic aspects of aging. Perhaps the author sensed this transformation when he goes on to say: "Providentially, as long as the blood vessels of the brain supply that extraordinarily delicate and sensitive structure with an abundant supply of oxygen and sugar, clarity of the mental processes is preserved and pleasant social relations, as well as cherished personal activities, can be continued."

Perhaps Dr. Cannon had a premonition of coming events when he quoted from Dr. Mitchell as the closing words of the book:

> "I know the night is near at hand.
> The mists lie low on hill and bay.
> The autumn sheaves are dewless, dry;
> But I have had the day."

ROBERT A. MOORE

BOOKS RECEIVED

Books received since April 1, 1946 are acknowledged in the following list. Insofar as space and time permit, some will be selected for review in a later issue, but it is unlikely that all will be reviewed.

Evolution of Plastic Surgery, by Maxwell Maltz, Froben Press, New York, 1946, $5.00, 368 pages.

Treatment of Arthritis and Rheumatism in General Practice, by Bernard Aschner, Froben Press, New York, 1946, $5.00.

Biogenergetics and Growth, by Samuel Brody, Reinhold Publishing Corporation, New York, 1945, $8.50, 1023 pages.

A Future of Preventive Medicine, by Edward J. Stieglitz, The Commonwealth Fund, New York, 1945, $1.00, 73 pages. (Reviewed in this issue, page 405.)

The Way of an Investigator, by Walter B. Cannon, W. W. Norton and Company, Inc., New York, 1945, $3.00, 229 pages. (Reviewed in this issue, page 406.)

Social Adjustment in Old Age. A Research Planning Report, Social Science Research Council, New York, 1946, 222 pages.

Ambulatory Proctology, by Alfred J. Cantor, Paul B. Hoeber, New York, 1946, $8.00, 524 pages.

INDEX TO CURRENT PERIODICAL LITERATURE

It is difficult to cover all journals and list all papers concerned with aging and the aged. Authors and publishers are requested to call attention to publications or send reprints. Editor

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ANEURYSM—Longevity with Ventricular Aneurysm. Sidney L. Penner and Michael Peters. *New England Journal of Medicine, 234:* 523–526, 1946.

ANTHONY, NORMAN—*How to Grow Old Disgracefully.* Duell, Sloan and Pearce, New York, 1946.

ALTMEYER, A. J.—Improving Old Age and Survivors Insurance. *Social Security Bulletin, 9:* 3–10, 1946.

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CANCER—Influence of Age on Total Epidermal Lipid During Carcinogenesis Induced by Methylcholanthrene in Mice. V. Suntzeff, E. V. Cowdry, and C. Carruthers. *Cancer Research, 6:* 179–182, 1946.

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DAVIDS, R. C.—Are You Growing Old Needlessly? *Better Homes and Gardens, 24:* 27, 1946.

DEMPSEY, EDWARD W.—(See Wislocki, George B., and Edward W. Dempsey.)

DIABETES—Diabetes and Geriatrics. Joseph H. Barach. *Clinics, 4:* 1096–1113, 1946.

DOUGLAS, GILEAN—Age is a Convention. *She, 4:* 40–43, 1946.

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